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A systematic review of blood biomarkers with individual participant data meta-analysis of matrix-metalloproteinase-7 in IPF

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Take home message:

Robust methodology using individual participant data meta-analysis demonstrates baseline MMP-7 levels predict overall mortality and disease progression in patients with untreated IPF independent of age, gender, smoking status and lung function.

ABSTRACT

Background

Blood derived biomarkers have been extensively described as potential prognostic markers in idiopathic pulmonary fibrosis (IPF), but studies have been limited by analyses using data-dependent thresholds, inconsistent adjustment for confounders and an array of endpoints, thus often yielding ungeneralisable results. Meta-analysis of individual participant data (IPD) is a powerful tool to overcome these limitations. Through systematic review of blood derived biomarkers, sufficient studies with measurements of Matrix Metalloproteinase-7 (MMP-7) were identified to facilitate standardised analyses of the prognostic potential of this biomarker in IPF.

Methods

Electronic databases were searched on 12th November 2020 to identify prospective studies reporting outcomes in patients with untreated IPF, stratified according to at least one pre-specified biomarker, measured at either baseline, or change over three months. Individual participant data (IPD) was sought for studies investigating MMP-7 as a prognostic factor. The primary outcome was overall mortality according to standardised MMP-7 z-scores, with a secondary outcome of disease progression in 12 months, all adjusted for age, gender, smoking and baseline FVC.

Results

IPD was available for nine studies out of twelve identified, reporting outcomes from 1664 participants. Baseline MMP-7 levels were associated with increased mortality risk (adjusted HR1.23, 95%CI 1.03;1.48, I^2=64.3%) and disease progression (adjusted OR1.27, 95%CI 1.11;1.46, I^2=5.9%). In limited studies, three-month change in MMP-7 was not associated with outcomes.

Conclusion

IPD meta-analysis demonstrated greater baseline MMP-7 levels were independently associated with an increased risk of poor outcomes in patients with untreated IPF, whilst short term changes did not reflect disease progression.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive fibrotic lung disease of unknown aetiology that affects approximately 3 million people worldwide, with a rising incidence and a median survival from diagnosis of approximately three years.[1-5] Disease trajectory is variable, ranging from slow progression to rapid loss of lung function and death.[6] The most recognised biomarker of disease progression in IPF is the change in forced vital capacity (FVC) at 12 months.[7 8] However, lung function measurements have limitations, including test variability related to patient effort and confounding effects of comorbidities such as emphysema.[9]

Blood derived biomarkers have been extensively described as potential prognostic markers that reflect disease severity, though none have been implemented into routine clinical practice. Studies of biomarkers have been limited by small sample sizes, inconsistent methodologies including inconsistent adjustment for confounding variables, a variety of endpoints, and analysis of outcomes using data-dependent biomarker thresholds, thus often yielding inconsistent and ungeneralisable results.[10 11]

Individual patient data (IPD) meta-analyses are considered the gold standard for collecting and synthesising evidence, offering a number of advantages over traditional aggregate methods, by enabling standardisation of analyses and outcomes, consistent adjustment for potential confounding factors and robust subgroup analyses according to patient

characteristics.[12 13] No published studies have utilised IPD to systematically synthesise the evidence for blood biomarkers in IPF. Through systematic review of blood derived biomarkers, sufficient studies with measurements of Matrix Metalloproteinase-7 (MMP-7) were identified to facilitate standardised analyses of the prognostic potential of this biomarker in IPF. Thus, we explore the association between MMP-7 measured at baseline and change over three months, and clinical endpoints including mortality and disease progression in adult patients with untreated IPF.

METHODS

The systematic review was conducted in accordance with a pre-specified protocol (PROSPERO registration number: CRD42019120402) and has been reported using PRISMA-IPD (Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Individual Participant Data) guidelines.[14]

Search strategy and study selection

Electronic database searches were carried out in MEDLINE (1946 to latest), Embase (1974 to latest), Google Scholar, the Cochrane Register of Controlled Trials and ClinicalTrials.gov, with the last search carried out on 12th November 2020. Keywords and controlled vocabulary terms for “idiopathic pulmonary fibrosis” and “biomarkers”, alongside search filters for prognostic studies were applied (Figure S1).[15] Hand searches of reference lists in retrieved articles were conducted to identify further studies. Unpublished and ongoing studies were identified by searching pre-print servers including medRxiv, bioRxiv and Wellcome Open Research.

Following searches, two reviewers screened through titles and abstracts before full text review independently. Disagreements were resolved by consensus with a third reviewer.

The review included all original prospective observational studies that reported outcomes in stable or exacerbating patients aged over 18 with anti-fibrotic naïve IPF, diagnosed according to contemporaneous consensus guidelines,[16-18] stratified according to at least one pre-identified blood biomarker. Conference abstracts reporting sufficient detail were eligible for inclusion. Retrospective studies, case reports, animal studies and studies investigating non-IPF interstitial lung disease (ILD) were excluded. Language or year of publication restrictions were not applied. No minimal study sample size was specified for inclusion.

Studies reporting the following biomarkers measured at either baseline and/or trends over 3 months were eligible for review: biomarkers of epithelial dysfunction including MMP-7, Krebs von den Lungen-6 (KL-6), surfactant protein-A (SP-A), surfactant protein-D (SP-D), matrix metalloproteinase-1 (MMP-1), cancer antigen 125 (CA-125), carbohydrate antigen 19-9 (CA19-9), vascular endothelial growth factor (VEGF), insulin like growth factor binding protein 2 (IGFBP2)], biomarkers of ECM modelling [collagen synthesis peptides, neoepitopes, lysyl oxidase like 2 (LOXL2), periostin, osteopontin] and biomarkers of immune dysregulation [C-C motif chemokine ligand 18 (CCL-18), chemokine ligand 13 (CXCL13), interleukin-8 (IL-8), heat shock protein 70 (HSP70), chitinase-3-like protein 1 (YKL40), intracellular adhesion molecule 1 (ICAM-1)].

Data extraction and risk of bias assessment

IPD were sought from corresponding authors of studies investigating MMP-7 as a prognostic factor, using secure and encrypted electronic mail communication. A minimum of three reminders, each four weeks apart were sent. Data from sponsored clinical studies were requested through various online portals.[19-21] Requested data included participant demographics (age, gender, smoking status and baseline lung function), baseline and three-month MMP-7 levels and outcomes including 12-month lung function and overall mortality (Figure S2).

Where IPD were not made available, aggregate data were extracted from study publications, using a proforma and verified by a second reviewer. Data included study design, participant and biomarkers characteristics, and outcome data including sample sizes, mean values and standard deviations of biomarkers in individuals with and without the event. Time to event data were collected using adjusted hazard ratios (HR) where reported.

Risk of bias assessment was carried out independently by two reviewers using the Quality in Prognostic Studies (QUIPS) tool.[22] The QUIPS tool assesses the risk of bias across six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis and reporting. All studies were included in the review irrespective of their risk of bias rating. The GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework was applied to rate the overall quality of evidence for each outcome.[23]

Statistical analysis

All identified studies were included in the data synthesis, with summary tables for study characteristics. Multiple cohorts within the same study were treated as individual cohorts. The primary outcome was overall mortality. Secondary outcomes measures included change in percent predicted FVC from baseline at 12 months and disease progression defined as 10% relative decline in FVC or death within 12 months of baseline. Hazard ratios (HR) for MMP-7 levels in predicting mortality, and odds ratios (OR) for predicting disease progression, were estimated using a two-stage IPD meta-analysis with random effects and presented as forest plots. Estimates were adjusted for *a priori* confounders including age, sex, smoking history, and baseline FVC. Unadjusted analyses have been presented in the supplementary material (Figure S10). Studies with a follow up duration longer than three years were censored for survival analyses. To standardise biomarker values across studies, z scores specific to each study were calculated and analysed as exposure variables. The change in MMP-7 over three-months was calculated where available using relative percent change from baseline. Participants with missing data were excluded using listwise deletion. The I^2 statistic was used to evaluate statistical heterogeneity between studies. Meta-regression was conducted where sufficient studies were included to explore variability in heterogeneity according to: study design (cohort vs. randomised trial), single-centre studies, non-peer reviewed manuscripts, assay methods (ELISA vs. non-ELISA), and the type of blood samples used (serum vs. plasma). Publication bias was assessed using funnel plot analysis and Egger's test.[24] All statistical analyses were performed using Stata 16 (Statacorp, Texas US). Due to methodological heterogeneity, marked difference in outcome measures and insufficient studies for IPD, biomarkers other than MMP-7 have been described narratively and in tables.

RESULTS

Searches of the electronic databases on 12th November 2020 yielded 4930 articles, with a further 69 studies identified through preprint servers. Following the removal of duplicates, screening and full text review, 29 studies published worldwide between 2007 and 2020, reporting outcomes from 3950 IPF participants were included (Figure 1). A total of 12 studies reported outcomes in relation to MMP-7, of which IPD was available for nine studies (75%) reporting data from eleven individual cohorts and 1664 participants (Table 1). No issues with the integrity of IPD were identified. A further 15 blood biomarkers were evaluated across the included studies, with a number of studies evaluating combinations of biomarkers (Table S1).

Risk of bias assessment of the retrieved studies identified limitations and a number of possible biases (Figure 2, Table S2). For studies included in the MMP-7 meta-analysis, publication bias was not detected statistically, but visual inspection of funnel plots suggested publication bias was present for some of the outcomes assessed. (Figure S3 and S4). Most MMP-7 studies defined the study population specifically with clear inclusion/exclusion criteria. Biomarkers were measured consistently using the same sample matrices (plasma or serum) across included participants in each study, although details of assay platforms used to measure the analytes were frequently unreported. Outcome data were measured objectively and applied consistently to all study participants. Studies evaluating biomarkers other than MMP-7 had similar limitations and risks of bias. Blood biomarkers are known to be influenced by age and sex, as well as possible lifestyle factors such as smoking, which along with baseline lung

function are all confounders upon disease outcome.[25] In approximately half of all included studies, possible confounders were not measured, and there was inconsistent adjustment in estimations where accepted confounders were measured. Moreover, in a number of studies, analyses were performed using data-dependent biomarker thresholds that were inconsistent across studies.

Association between blood biomarkers and clinical outcomes

Baseline blood biomarkers that predict mortality

Ten studies evaluated the relationship between mortality and MMP-7, with IPD available for eight studies totalling 1492 participants. Meta-analysis demonstrated greater baseline MMP-7 values were associated with a 23% increased risk of overall mortality [adjusted HR (aHR) 1.23 per standard deviation (SD) increase, 95%CI 1.03;1.48, I^2=64.3%) (Figure 3A), though there was substantial statistical heterogeneity which could not be explained by variability in the factors assessed (Table S3). When mortality at 12 months was examined specifically, baseline MMP-7 levels were inconclusively associated with death (aHR 1.33 per SD increase, 95%CI 0.99;1.78, I^2=59.6%) (Figure 3B). Applying the GRADE framework, we rate the confidence in mortality estimates with moderate certainty (Table S4). Where IPD was unavailable, MMP-7 values above 5.7ng/mL were associated with increased mortality (aHR 2.18 95%CI 1.1;4.32) over a median follow up of 19 months in a study of 438 participants.[26] A further study of 57 participants found MMP-7 levels did not predict death[27] (Table S5).

The primary outcome of mortality was evaluated for a further 14 biomarkers in a total of 17 studies not assessed in IPD meta-analysis, with inconsistent and inconclusive findings (Figure 6 and Table S5). Study follow up times were inconsistent, effect sizes varied with wide confidence intervals, and estimates were often unadjusted for important covariates.

Change in biomarkers predicting mortality

Three studies totalling 498 participants explored the association between MMP-7 change over three months and mortality.[28 29] IPD meta-analysis showed no association with mortality (aHR 1.00, 95%CI 0.99;1.02,I^2=53.3%), nor when mortality was censored at 12 months (aOR 1.00, 95%CI 0.99;1.01,I^2=37.4%) (Figures S5 and S6).

Three publications from the same cohort evaluated the relationship between longitudinal biomarker measurement and mortality.[30-32] In both discovery and validation cohorts, a rise in CA-125 over three-months doubled the risk of death, but the remaining biomarkers were not predictive of mortality (Figure 6 and Table S6). A validation cohort of 145 participants demonstrated replication of rising neoepitopes degraded by matrix metalloproteinases (C1M, C3M, C6M and CRPM), but the rate of change of collagen synthesis peptides was not associated with mortality.[32]

Baseline biomarkers that predict disease progression and change in FVC

Ten studies measured MMP-7 levels as markers of disease progression, with eight studies totalling 1383 participants included in the IPD meta-analysis. Meta-analysis demonstrated baseline MMP-7 was associated with disease progression (aOR 1.27 per SD increase, 95%CI 1.11;1.46,I^2=5.9%) (Figure 4). Whilst heterogeneity was low, meta-regression identified sample assay techniques (ELISA vs. other) to be a source of heterogeneity. In subgroup analysis according to assay, the odds ratio for disease progression was estimated at 1.56 per SD increase (95%CI 1.26;1.82, I^2=0%) when restricted to studies using ELISA (Figure S7). When the relationship between baseline MMP-7 and relative change in FVC at 12 months was examined specifically in six studies of 891 participants, meta-analysis indicated that a 1 standard deviation greater baseline MMP-7 was associated with a -0.85% relative change in 12-month FVC percent predicted (95%CI -1.65; -0.05, I^2=0%) (Figure 5). We assess findings for disease progression and change in FVC outcomes with high certainty (Table S4). For studies not included in IPD meta-analysis, baseline MMP-7 values above 3.8ng/mL doubled the risk of disease progression (aHR 2.2 95%CI 1.4;3.7) over a median follow-up of 19 months in 211 participants.[33] In a further study of 57 participants, MMP-7 did not predict disease progression (Table S7).

Disease progression was evaluated for a number of other biomarkers in 19 studies that were not included in IPD meta-analysis. None were consistently predictive of disease progression, though there was significant heterogeneity in adopted definitions of disease progression, with lung function indices, mortality, transplant and acute exacerbations included in various combinations at non-unified time points (Figure 6 and Table S7, S8).

Change in biomarkers predicting disease progression

Three studies totalling 481 participants investigating the association between MMP-7 change over three months and disease progression were included in IPD meta-analysis. Change in MMP-7 over three-months was not associated with disease progression (aOR 1.00 per percent increase, 95%CI 0.99;1.01, I^2=22.5%) (Figure S8), nor with change in FVC over 12 months (effect size 0.01% increase per percent MMP-7 increase 95%CI -0.07;0.08, I^2=60.8%) (Figure S9). In a study of 211 participants not included in IPD meta-analysis, a two-fold change in MMP-7 over four months was associated with doubling the risk of disease progression.[33]

In one study, participants with progressive disease had rising concentrations of CA-125 over 3 months compared to those with stable disease, but no relationship was replicated for other biomarkers.[30] (Figure 6, Table S9)

Discussion

This systematic review of prospective studies in patients with untreated IPF identified 16 blood derived biomarkers and assessed 6 outcome variables, but there were only sufficient studies to undertake an IPD meta-analysis for MMP-7. IPD meta-analysis demonstrated baseline MMP-7 levels predicted all-cause mortality and disease progression and correlated with FVC percent predicted change over 12 months. There was a 23% greater risk of overall mortality and 27% greater risk of disease progression, per standard deviation increase in baseline MMP-7 values. An inconclusive association was observed for risk of 12-month

mortality. Notably, MMP-7 levels did not seem to change longitudinally over three months, with no association observed with any of the measured outcomes. However, a study not included in quantitative synthesis suggested that in those individuals where MMP-7 does rise, there may be an associated risk in progression[33]. Mortality outcomes were rated with moderate certainty and disease progression and change in FVC outcomes with high certainty (Table S4).

Our IPD meta-analysis represents the first time it has been possible to synthesise blood biomarker findings in IPF. The meta-analysis was focused on MMP-7 as there were sufficient studies available, however individually these had yielded inconsistent results, reported data-dependent thresholds and often not adjusted for confounding factors. IPD enabled analysis of MMP-7 levels as continuous variables transformed to z-scores to overcome assay variability, supported standardised definition of outcomes, and consistent adjustment for important covariates, which enabled robust and reliable conclusions. We performed two-stage IPD meta-analysis, which does not assess study estimate and effects simultaneously although is considered to produce unbiased estimates,[34] and enabled modelling IPD from 1492 participants across separate secure servers and portals. Analysis of heterogeneity in IPD meta-analysis indicated that assay type was a significant contributor to heterogeneity, particularly in estimates of disease progression.

There are limitations to this review. Whilst language restrictions were not applied, two articles in Japanese were excluded as they could not be translated to English to assess inclusion criteria. We included only those studies where participants were diagnosed according to international consensus guidelines, supporting the robustness and generalisability of our

findings. We excluded studies in IIPs not specific to IPF, which limits interpretation in non-IPF ILDs, although ongoing studies exploring shared mechanistic pathways will provide further insight.[35] Furthermore, by focussing on untreated IPF patients our results do not address the theranostic value of MMP-7 in relation to anti-fibrotic therapy. There was significant statistical heterogeneity in some of the outcomes, and therefore these should be interpreted with caution. We were unable to explain all the residual heterogeneity using the factors we assessed. IPD was not obtained from a limited number of suitable studies, and therefore we had to report these findings narratively.

Biomarkers of disease activity have the potential to facilitate clinical management and transform early-phase clinical trials by acting as surrogate endpoints. Dysfunctional epithelial cells contribute to fibrogenesis by secreting profibrotic mediators including matrix-metalloproteinases (MMPs),[36] responsible for degrading multiple components of extracellular matrix, activating biological mediators, and facilitating epithelial-mesenchymal transition.[37] Further research could elucidate the relationship between IPF pharmacotherapy and MMP-7, particularly to identify whether changes in MMP-7 levels may represent a biomarker of therapeutic response. From a clinical perspective, MMP-7 should be considered for implementation as a prognostic tool at the point of diagnosis, especially where lung function testing is cumbersome or unavailable.

Due to heterogeneity in study designs and reported outcomes, there were insufficient data for quantitative analysis in non-MMP-7 studies. Whilst many biomarkers showed an association with mortality in single studies, replication of effects across studies was weak. We highlight sources of considerable bias and variability. Studies were typically observational, of

relatively modest size with a lack of prespecified power calculations. A number of different laboratory techniques were applied to measure biomarker levels across studies, with very few studies reporting detailed assay information, particularly with regards to measures of precision, and there was inconsistency in thresholds defining positive and negative biomarker result. Short-term changes in biomarker concentrations over three-months were often not associated with specified clinical outcomes suggesting further studies are needed before such biomarkers can be adopted clinically. Further biomarker research should focus on rigorously designed longitudinal studies with discovery and validation cohorts, using validated biomarker assays and standardised endpoints. Furthermore, it is possible that combinations of biomarkers will add granularity to our understanding of pathogenesis and prognosis of IPF and further studies evaluating their utility are needed. As further studies are published, IPD meta-analysis should be considered to produce more reliable results and support generalisability.

In summary, whilst a number of other blood biomarkers have been studied for predicting prognosis, there is currently insufficient replication to enable adoption into clinical testing, with the possible exception of MMP-7. We apply robust methodology and IPD meta-analysis to demonstrate baseline MMP-7 levels predict overall mortality and disease progression in patients with untreated IPF independent of age, gender, smoking status and lung physiology. However, short term changes in MMP-7 over three-months offered limited prognostic value in the absence of an empirical threshold.

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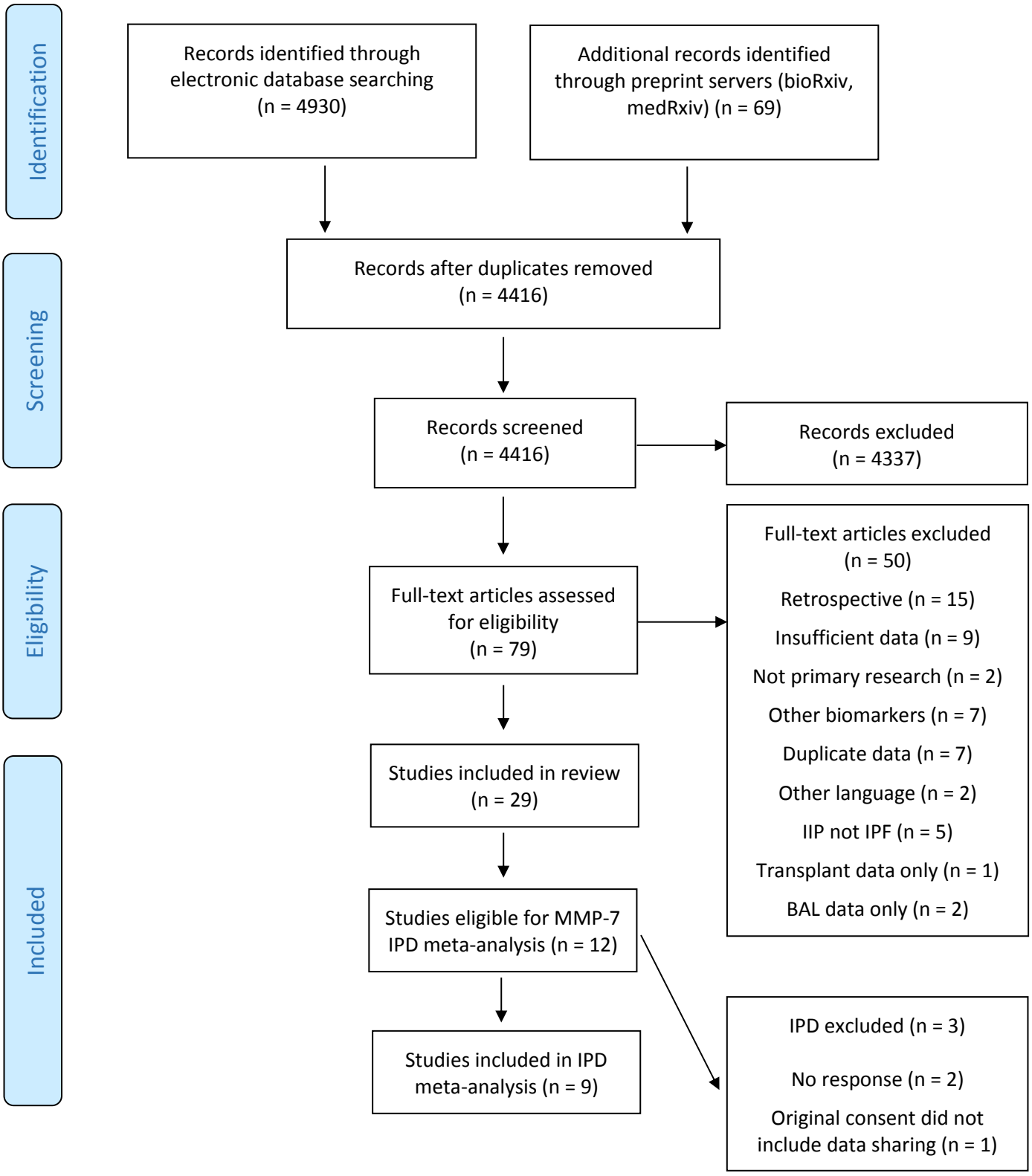


Figure 1 - Flow diagram illustrates systematic search and screening strategy, including numbers of studies meeting eligibility criteria and numbers excluded.

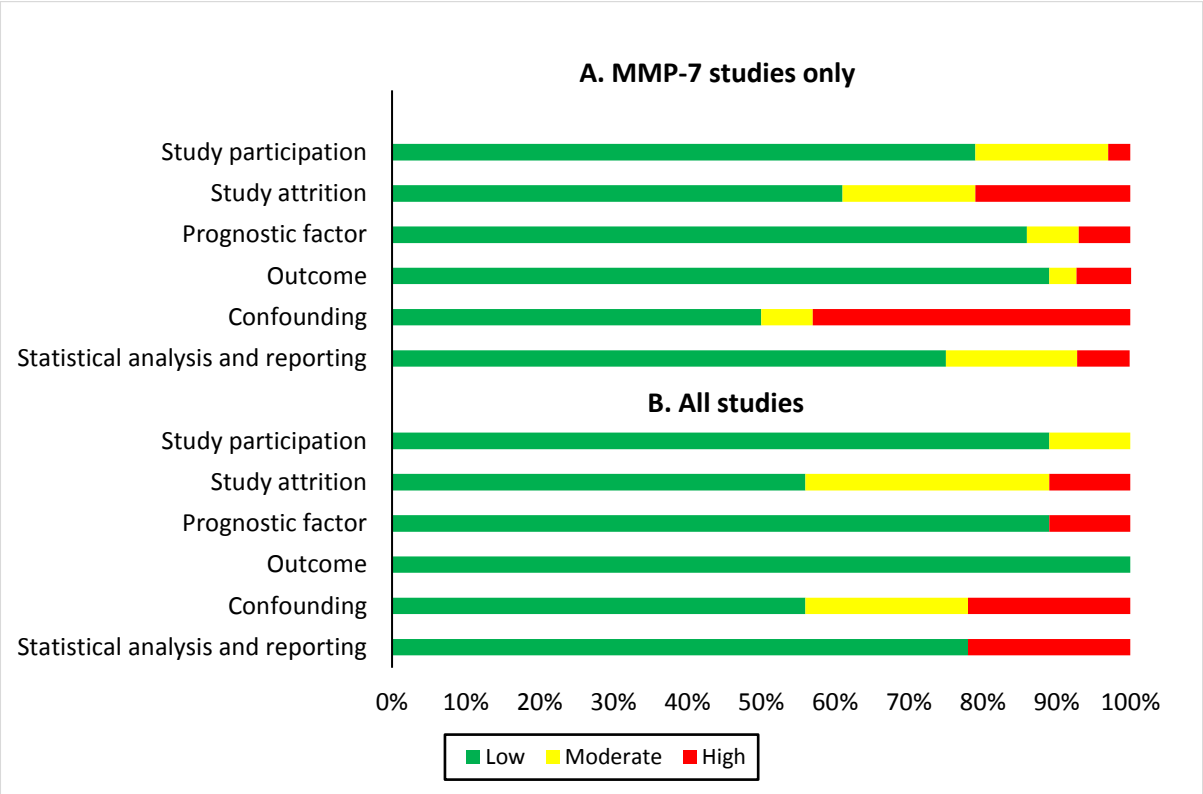


Figure 2 – Risk of bias assessment for A. MMP-7 studies only B. All included studies. The risk of bias across studies was rated as low, moderate or high risk in six categories using the QUIPs tool.

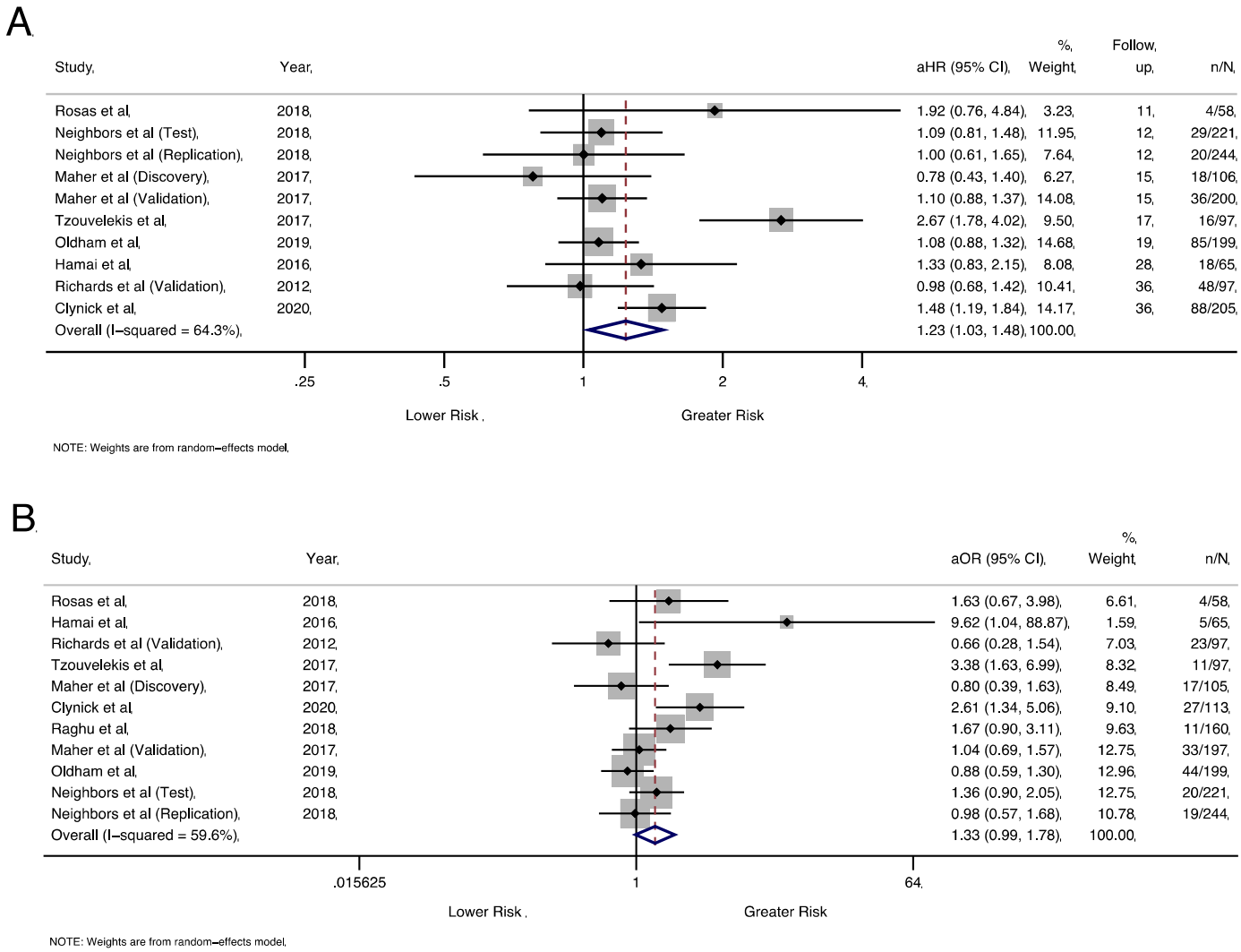


Figure 3 - Mortality forest plot.

A – Overall mortality. B: Mortality at 12 months. Adjusted effect sizes with 95% confidence intervals per standard deviation increase in baseline MMP-7. Study follow up time shown in months. n denotes the number of deaths, and N represents the total number of participants included per study. All estimates were adjusted for age, sex, smoking status, and baseline FVC.

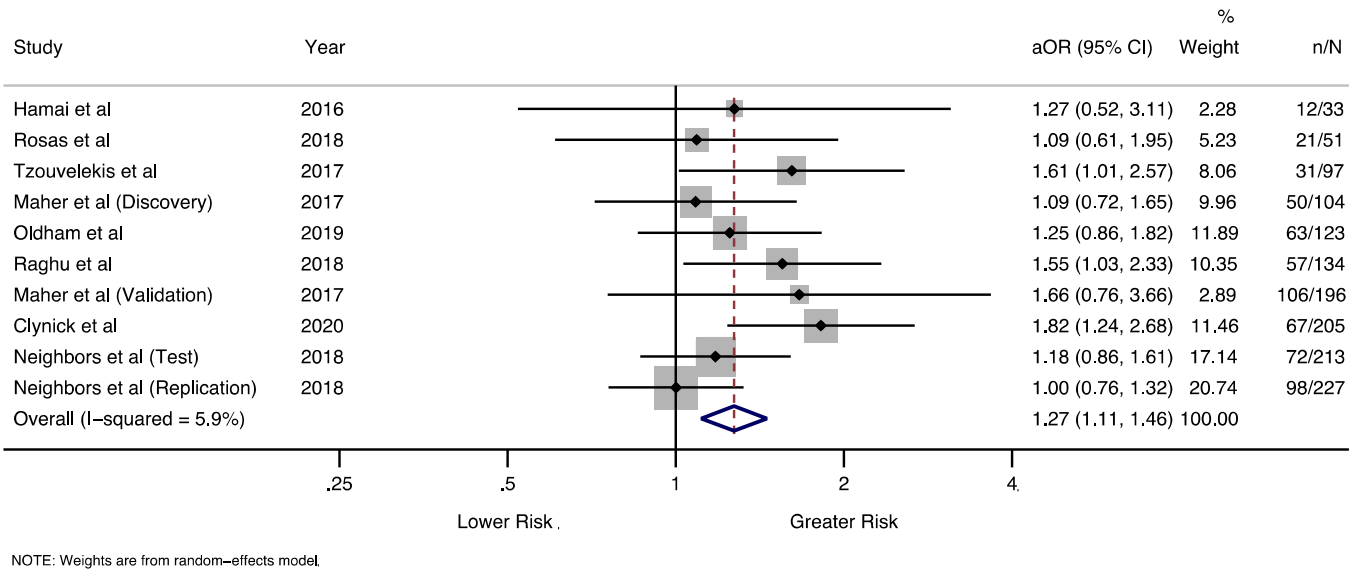


Figure 4 – Disease progression forest plot.
Pooled adjusted odds ratios with 95% confidence intervals for risk of disease progression, per standard deviation increase in baseline MMP-7. n denotes the number of progressors, and N represents the total number of participants included in the analysis per study. All estimates were adjusted for age, sex, smoking status, and baseline FVC.

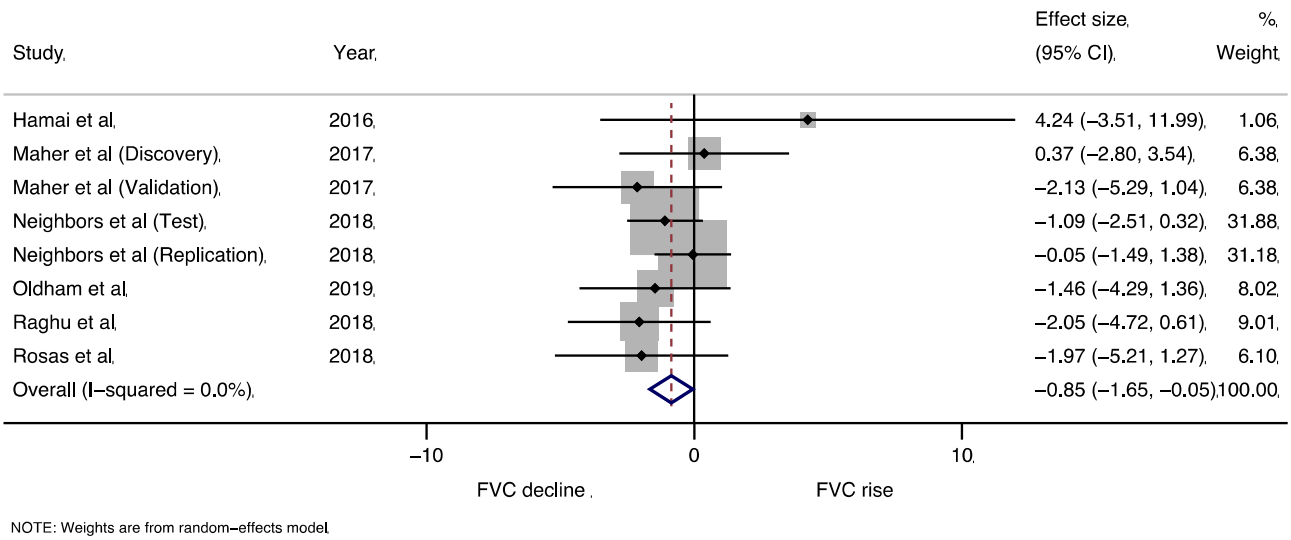


Figure 5 – Relative change in FVC% percent predicted forest plot

Pooled effect size with 95% confidence intervals for FVC% percent predicted relative change at 12 months, per standard deviation increase in baseline MMP-7. All estimates were adjusted for age, sex, smoking status, and baseline FVC.

Biomarker	Mortality	Change in biomarkers predicting mortality	Disease progression	Change in biomarkers predicting disease progression	FVC change	Change in biomarkers predicting FVC change
SP-A		-		-		-
SP-D						-
KL-6		-				-
CA-125					-	-
CA19-9					-	-
LOXL2		-		-	-	-
Periostin		-		-		-
CCL-18		-		-		-
CXCL-13		-		-		-
IL-8				-	-	-
YKL-40		-		-		-
ICAM-1				-	-	-
IGFBP-2	-		-	-	-	-

Figure 6 – Summary of study results. Each dot represents a study (or individual cohort in studies with more than one cohort). Green dots represent studies showing an association between the biomarker and outcome, and red dots represent studies where no association was found. Larger circles represent studies with a sample size > 100 participants, and smaller circles represent studies with sample sizes smaller than 100 participants. Outcomes where no studies were found for the listed biomarker are represented with a dash (-).

Author and year of publication	Included in IPD MA	Country of study	IPF Sample size	Study follow up, months (median, IQR)	Age (years)	Sex – male (%)	Baseline FVC % predicted	Baseline DL_{CO} % predicted	Relevant outcomes reported
Bauer, 2017[33]	No	multi-national	211 (BUILD-3[38])	NR	63.1 (8.9)	64	75.7 (10.7)	47.7 (10.7)	Disease progression (FVC≥10% decline, DL_{CO} ≥ 15%, acute exacerbation or death) up to end of study, change in FVC at 4 months
Hamai, 2016[39]	Yes	Japan single centre	65	28 (16-45)	69.3 (8.6)	77	75.6 (21.9)	47.1 (15.8)	5-year mortality
Maher, 2017[30]	Yes	UK multi-centre	106 (Discovery)	15 (15-15)	70.8 (8.3)	78	79 (18.9)	43.3 (14.8)	Overall mortality, disease progression at 12 months (all-cause mortality or FVC decline ≥ 10%)
	Yes		200 (Validation)	15 (15-15)	72.5 (7.7)	76	81.4 (19.2)	49 (16.9)	
Navaratnam, 2014/Clynick , 2020[40 41] #	Yes	UK multi-centre	205	42 (20-60)	73.2 (8.7)	74	84.7 (18.7)	43.7 (15.8)	Overall mortality, disease progression at 12 months (all-cause mortality or >10% FVC decline)
Neighbors, 2018[29]	Yes	multi-national	221 CAPACITY [42]	18 (17-21)	66.9 (7.4)	72	73.4 (13.4)	46.5 (9.4)	At 12 months: Disease progression (FVC ≥10% absolute decline or death), change in FVC, death
	Yes		244 ASCEND [43]	12 (11-12)	67.7 (7.2)	77	68.3 (10.9)	43.9 (11.9)	
Oldham, 2019	Yes	USA multi-centre	199	19 (8-32)	71.5 (8.9)	74	68.5 (19.1)	48.5 (20.4)	24-month transplant-free survival, overall mortality
Peljto, 2013[44]	No	multi-national	438 (INSPIRE[45])	19 (14-25)	66.6 (7.5)	74	72.2 (12.4)	47.3 (8.9)	Overall mortality
Raghu, 2018[46]	Yes	multi-national	154	12 (12-12)	67.9 (8.4)	64	71.5 (19.6)	40.9 (15.9)	Disease progression at 52 weeks (FVC decrease ≥10% predicted or DL_{CO} decrease > 15% or lung transplantation or death)
Richards, 2012[47]	No	USA single centre	140 (Derivation)	22 (19)[c]	67.2 (8.3)	72	62 (19.6)	44.8 (17.1)	Overall mortality, disease progression (FVC relative decline ≥ 10% within any 1 year of follow up)
	Yes		97 (Validation)	42 (14-60)	68 (8.7)	66	60.8 (17)	45.4 (19)	
Rosas, 2018[48]	Yes	USA multi-centre	58	11 (11-12)	67.6 (7.3)	81	71.1 (15.6)	41.5 (13.9)	Change in FVC
Sokai, 2015[49]	No	Japan single centre	57	15 (0.4-61) [a]	69.4 (8.5)	90	84.2 (21.3)	43.7 (14.2)	Overall mortality, disease progression (death, FVC decline ≥ 10%, DL_{CO} ≥ 15% decline, admission due to respiratory failure) at 6 months
Tzouvelekis , 2017[50]	Yes	USA single centre	97	17 (8-17)	70 (8)	79	70.2 (16.5)	47.2 (16.9)	Overall mortality, disease progression (FVC decline > 10% predicted over study period)

Table 1 – Methodological characteristics of MMP-7 included studies with baseline participant characteristics and outcome data. Age, baseline FVC and baseline DL_{CO} reported as mean (standard deviation) unless otherwise stated. Study follow up time reported in median (IQR) unless otherwise stated.
DL_{CO}, gas transfer for carbon monoxide; FVC, forced vital capacity; [a] = median and range; [b] = median and IQR, [c.] = mean (SD)
= Post-hoc analysis (Clynick et al 2020) of Navaratnam et al, 2014. Original study did not report biomarker data

Supplementary Material

Figure 1 - MEDLINE search strategy

Figure 2 – Letter to authors for individual participant data

Figure 3 – Funnel plots for baseline MMP-7

Figure 4 – Funnel plots for change in MMP-7 over 3 months

Figure 5 – Forest plot for change in MMP-7 over 3 months and overall mortality

Figure 6 – Forest plot for change in MMP-7 over 3 months and 12 months mortality

Figure 7 – Forest plot for baseline MMP-7 and disease progression separated by ELISA and non-ELISA

Figure 8 – Forest plot for change in MMP-7 over 3 months and disease progression

Figure 9 – Forest plot for change in MMP-7 over 3 months and relative change in FVC at 12 months

Figure 10 – Forest plot for baseline MMP-7 and mortality and disease progression in unadjusted analyses

Table 1 – Methodological characteristics of non-MMP7 studies

Table 2 – Risk of bias for included studies per individual study

Table 3 – Meta-regression for variables assessed

Table 4 – GRADE rating

Table 5 – Table of mortality outcomes for baseline biomarkers

Table 6 – Table of mortality outcomes for short term change in biomarkers

Table 7 – Table of disease progression definition and outcomes for baseline biomarkers

Table 8 – Table of FVC change definitions and outcomes for baseline biomarkers

Table 9 – Table of disease progression definitions and outcomes for short term change in biomarkers

Participants	Intervention	Intervention	Outcomes
1. idiopathic pulmonary fibros*.mp.	12. Mucin-1/	45. Chitinase-3-Like Protein 1/ or Chitinase-3-like protein 1.mp.	78. prognosis.sh.
2. pulmonary fibros*.mp.	13. KL-6.mp.	46. IGFBP-2.mp. or Insulin-Like Growth Factor Binding Protein 2/	79. diagnosed.tw.
3. Pulmonary Fibrosis/ or Idiopathic Pulmonary Fibrosis/	14. krebs von den lungen-6.mp.	47. Insulin like growth factor binding protein 2.mp.	80. cohort:.mp.
4. cryptogenic fibrosing alveolitis.mp.	15. SP-A.mp.	48. ICAM-1.mp. or Intercellular Adhesion Molecule-1/	81. predictor:.tw.
5. usual interstitial pneumonia*.mp.	16. Pulmonary Surfactant-Associated Protein A/	49. VEGF.mp. or Vascular Endothelial Growth Factor A/	82. death.tw.
6. Fibrosing alveolitis.mp.	17. Pulmonary Surfactant-Associated Protein D/	50. HSP70 HEAT-SHOCK PROTEINS/ or HSP70.mp.	83. exp models, statistical/
7. Idiopathic Interstitial Pneumonia*.mp.	18. Pulmonary Surfactants/	51. LEPTIN/ or Leptin.mp.	84. disease progression.sh.
8. Interstitial pneumonia*.mp.	19. SP-D.mp.	52. CXCL13.mp. [mp=title, abstract, original title, name of substance	85. disease progression.mp.
9. Idiopathic interstitial lung disease.mp.	20. surfactant protein*.mp.	53. Chemokine CXCL13/ or C-X-C motif chemokine 13.mp.	
10. Chronic interstitial pneumonia*.mp.	21. CA-125 Antigen/ or CA125.mp.	54. Forced Vital Capacity.mp. or Vital Capacity/	
	22. cancer antigen 125.mp.	55. FVC.mp.	
	23. mucin 16.mp.	56. Forced Expiratory Volume/ or FEV1.mp.	
	24. CA-19-9 Antigen/ or CA19-9.mp.	57. forced expiratory volume.mp.	
	25. cancer antigen 19-9.mp.	58. 6-minute walk.mp.	
	26. carbohydrate antigen 19-9.mp.	59. Six-minute walk.mp.	
	27. Matrix Metalloproteinase 1/ or MMP-1.mp.	60. Walk Test/	
	28. Matrix Metalloproteinase 7/ or MMP-7.mp.	61. walk test.mp.	
	29. matrix metalloproteinase.mp. or Matrix Metalloproteinases/	62. 6MWT.mp.	
	30. LOXL2.mp.	63. 6MWD.mp.	
	31. Protein-Lysine 6-Oxidase/	64. Pulmonary diffusing capacity.mp. or Pulmonary Diffusing Capacity/	
	32. protein-lysine 6-oxidase.mp.	65. Diffusion capacity for carbon monoxide.mp.	
	33. periostin.mp.	66. DLCO.mp.	
	34. Osteoblast-specific factor 2.mp.	67. Transfer factor.mp. or Transfer Factor/	
	35. Epitopes/ or Neoepitope*.mp.	68. Gas transfer.mp.	
	36. Chemokines, CC/ or CCL18.mp.	69. TLCO.mp.	
	37. Chemokine CCL18.mp.	70. KCO.mp.	
	38. Chemokines, CC/ or CC-chemokine ligand 18.mp.	71. PHYSIOLOGY/	
	39. IL-8.mp. or Interleukin-8/	72. Physiolog*.mp.	
	40. Interleukin-8.mp.	73. SPIROMETRY/	
	41. CXCL8.mp.	74. spiromet*.mp.	
	42. Chemokine ligand 8.mp.	75. biomarkers.mp. or BIOMARKERS/	
	43. Chitinase-3-Like Protein 1/ or YKL-40.mp.	76. ((Serum or clinical or immun* or lab or laboratory or biochemical or biological) and marker*).mp.	
	44. CHI3L1.mp.		

Supplementary Figure 1 – MEDLINE search strategy (last search carried out on 12th November 2020). "OR" was used to combine search terms within each PICOS category, with "AND" used to combine search terms across PICOS categories.

Copy of email sent to authors

We would be very grateful for your assistance in undertaking a robust meta-analysis. The team at University of Nottingham (UK), led by Prof Gisli Jenkins, are conducting a systematic review and meta-analysis of blood biomarkers in IPF. The protocol for the study can be found on PROSPERO: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=120402

As part of the review, we will conduct a meta-analysis of the association of MMP-7 levels with mortality in IPF. We have chosen this biomarker because there is sufficient published data to make it feasible and useful.

To assist with this, we would be extremely grateful if you could kindly provide us with individual patient data from your highly relevant study entitled "…" published in …

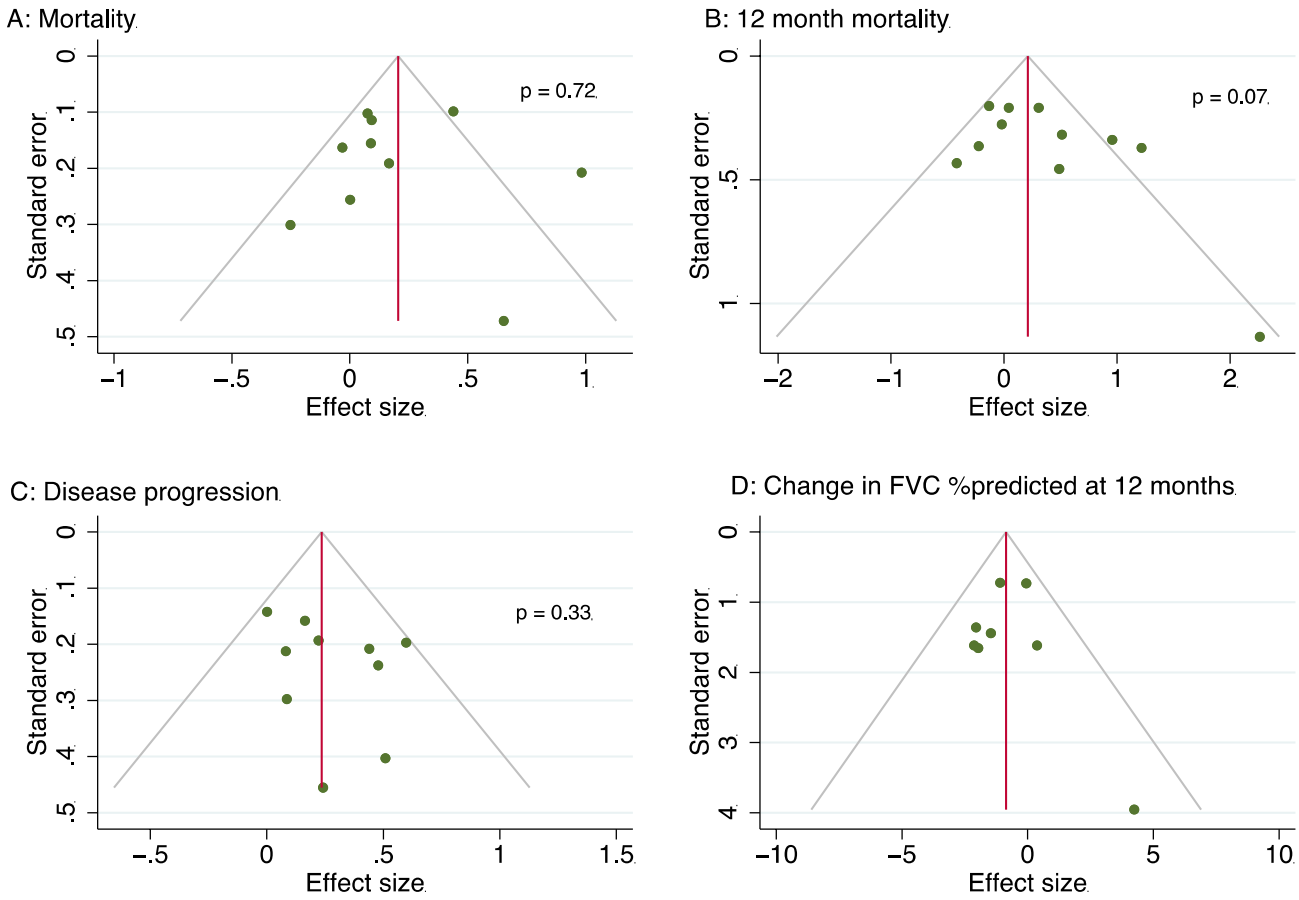
We also note significant heterogeneity in disease progression definitions across individual studies, and therefore hope to meta-analyse MMP-7 level associations with a shared definition based on FVC and mortality and would also appreciate data to assist with this. We appreciate the inconvenience such requests entail, and we would like to make the process as smooth as possible, we will of course acknowledge all support.

The attached excel spreadsheet highlights the anonymised data we are seeking for each patient, where available:

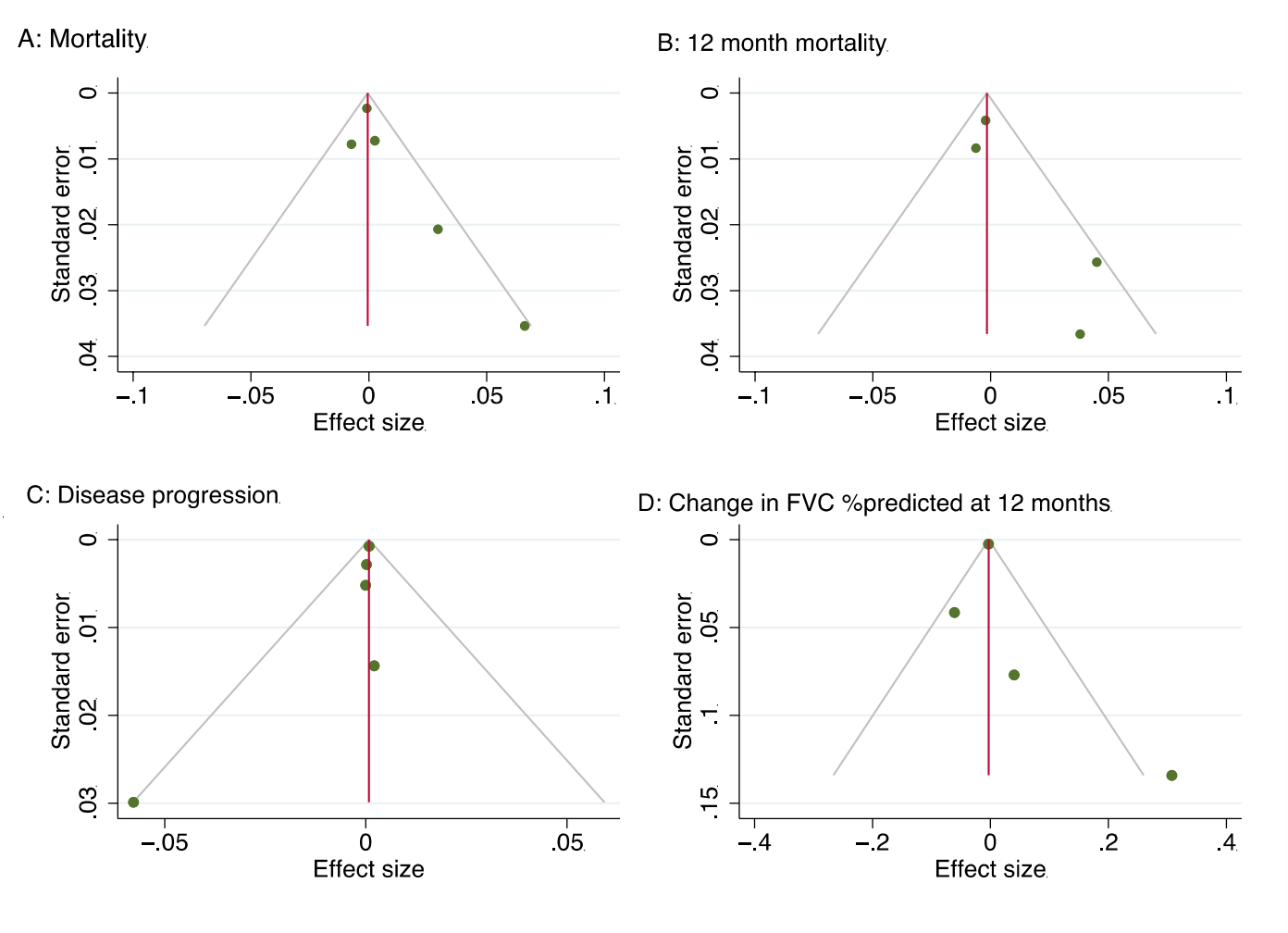
- MMP-7 level (baseline and 3-months)
- Assay method (type of assay used)
- Sample type (serum or plasma)
- Age
- Gender (M or F)
- Follow up time (days)
- Dead or alive at end
- Time to death (days)
- Baseline FVC (% predicted)
- 3-month FVC (% predicted)
- 12-month FVC (% predicted)
- Smoking (ever or never)

Thank you for your help, we look forward to communicating with you further.

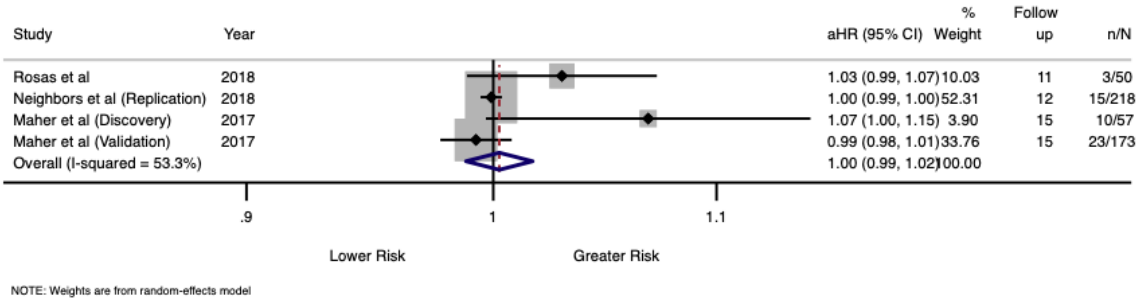
Supplementary Figure 2 – copy of message sent to authors for individual participant data. A minimum of three reminders, 4 weeks apart were sent.



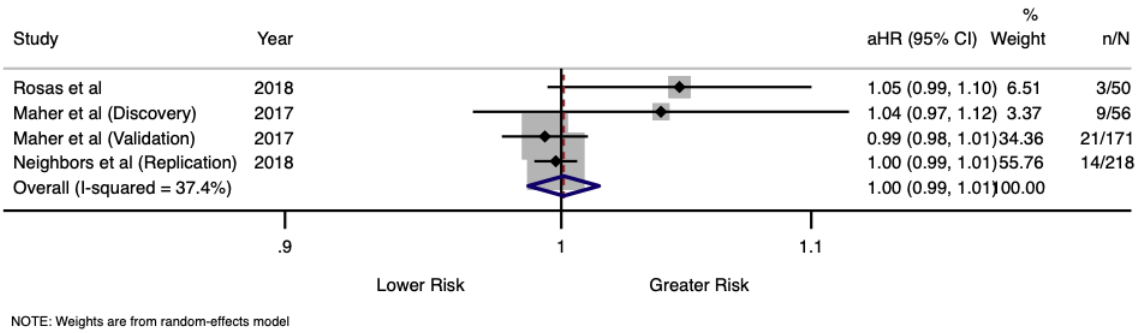
Supplementary Figure 3 – Funnel plots for outcomes evaluated in baseline MMP-7 IPD meta-analysis. A: overall mortality, B: 12-month mortality, C: Disease progression, D: Change in percent predicted FVC at 12 months. Publication bias assessed using Egger's test for outcomes with at least ten studies, and p values presented next to funnel plot.



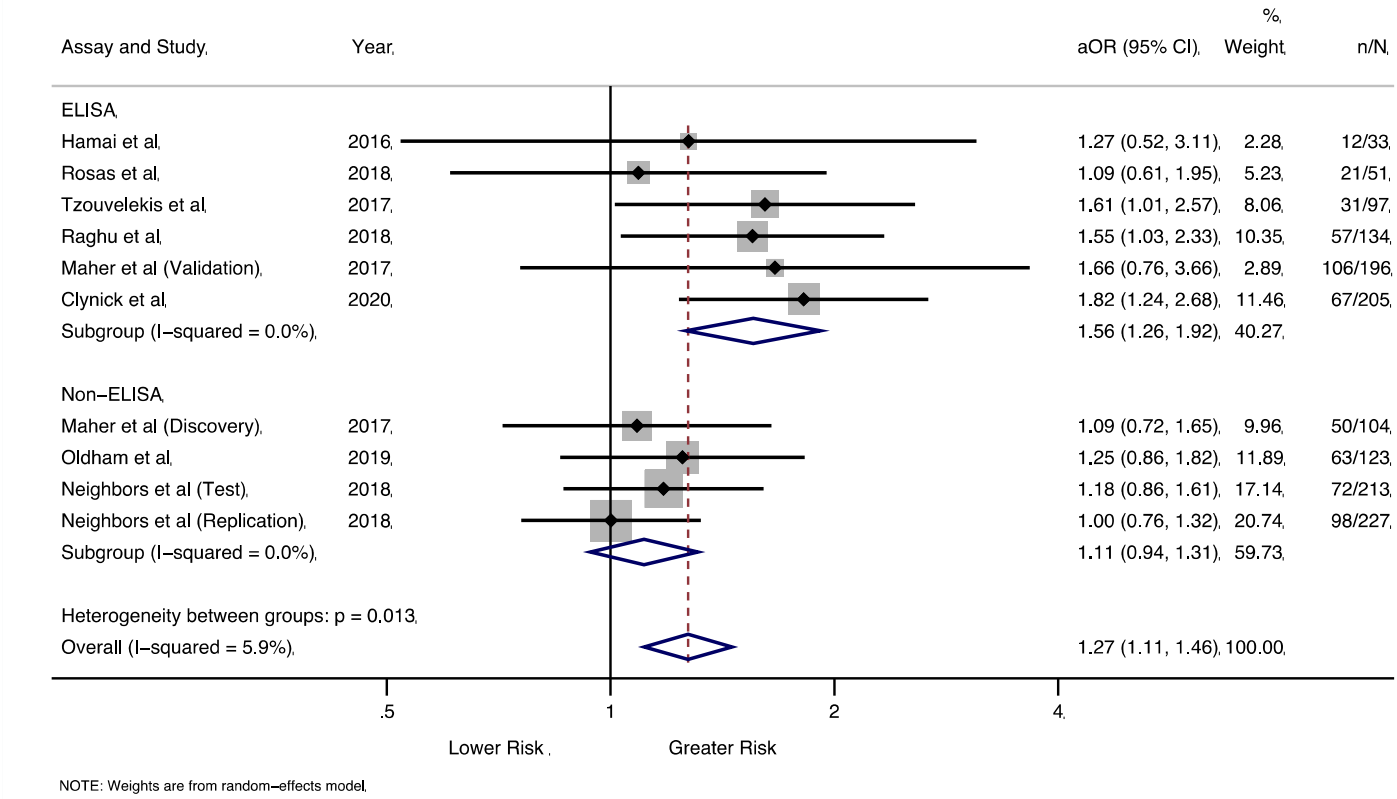
Supplementary Figure 4 – Funnel plots for outcomes evaluated for three-month change in MMP-7 IPD meta-analysis. A: overall mortality, B: 12-month mortality, C: Disease progression, D: Change in percent predicted FVC at 12 months.



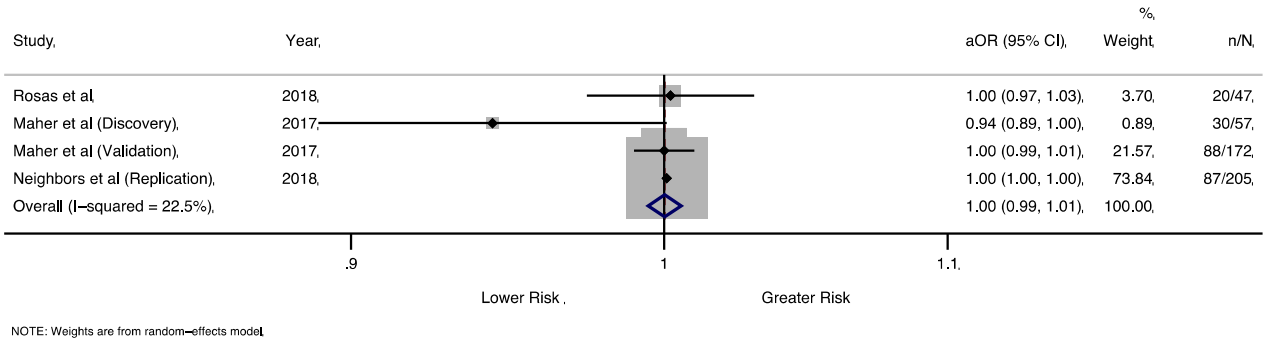
Supplementary Figure 5 - Pooled hazard ratios with 95% confidence intervals for risk of overall mortality, per percent relative increase in MMP-7 from baseline to three months. Study follow up time shown in months. n denotes the number of deaths, and N represents the total number of participants included per study.



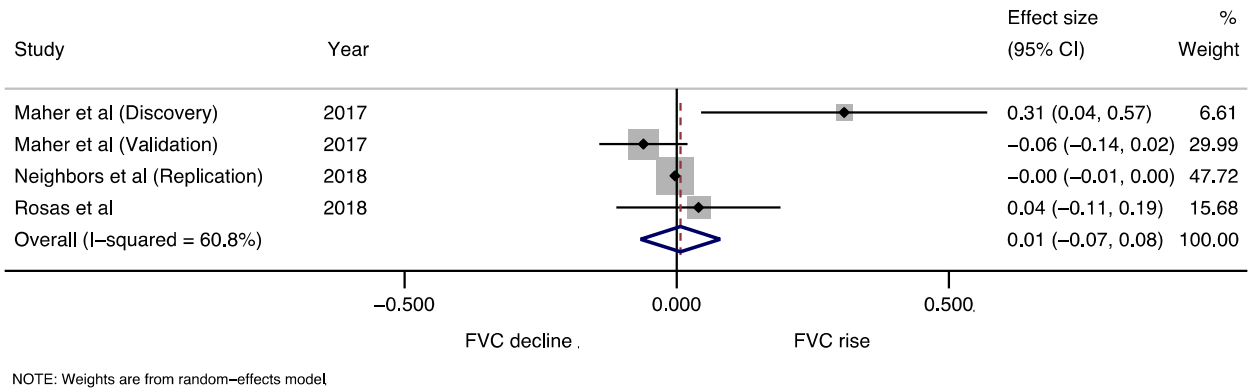
Supplementary Figure 6 - Pooled hazard ratios with 95% confidence intervals for risk of mortality at 12 months, per percent relative increase in MMP-7 from baseline to three months. n denotes the number of deaths, and N represents the total number of participants included per study.



Supplementary Figure 7 – Pooled odds ratios with 95% confidence intervals for risk of disease progression, per standard deviation increase in baseline MMP-7. Separated by ELISA and non-ELISA measurements. n denotes the number of progressors, and N represents the total number of participants included in the analysis per study.

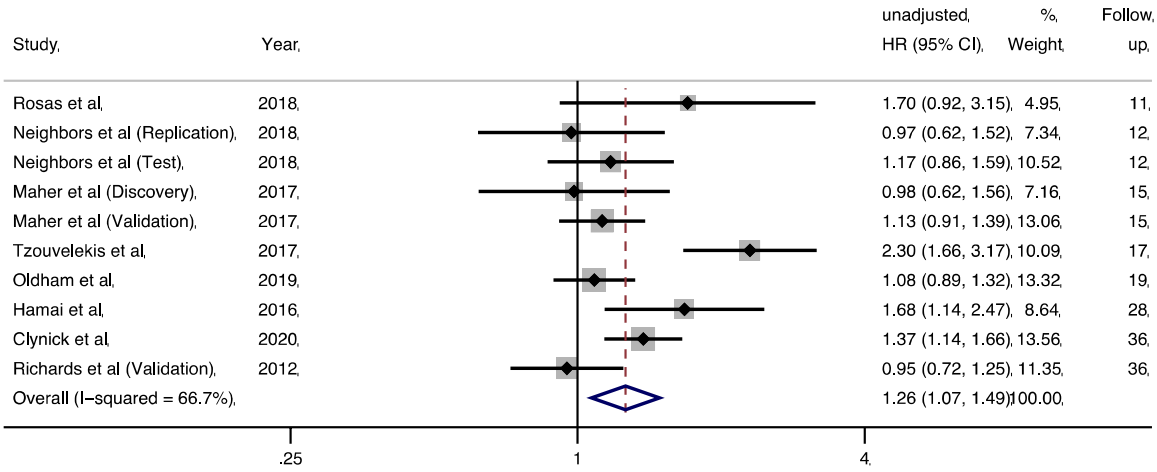


Supplementary Figure 8 – Pooled odds ratios with 95% confidence intervals for risk of disease progression, per percent relative increase in baseline MMP-7 to three months. n denotes the number of progressors, and N represents the total number of participants included in the analysis per study.

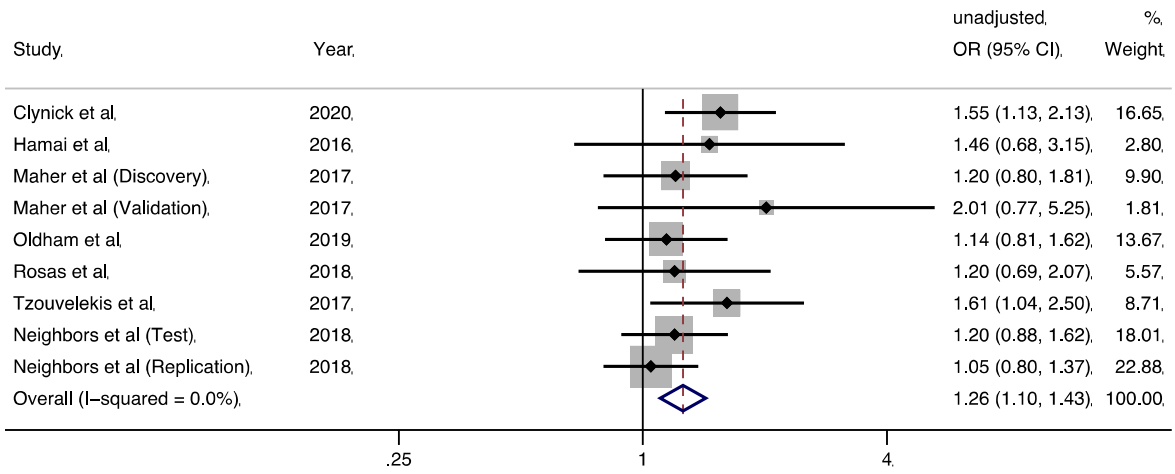


Supplementary Figure 9 – Pooled effect size with 95% confidence intervals for relative change in FVC at 12 months, per percent relative increase in baseline MMP-7 to three months.

A.



B.



Supplementary Figure 10 – Unadjusted analyses including pooled estimates with 95% confidence intervals for association of baseline MMP-7 per standard deviation increase and A. Mortality, B. Disease progression.

Author and year of publication	Country of study	IPF Sample size	Study follow up, months	Age (years)	Sex – male (%)	Baseline FVC % predicted	Baseline DL_{CO} % predicted	Relevant Biomarkers evaluated	Relevant outcomes reported
Bauer, 2017[33]	multi-national	211 (BUILD-3[38])	NR	63.1 (8.9)	64	75.7 (10.7)	47.7 (10.7)	collagen synthesis peptides	Disease progression (FVC≥10% decline, DL_{CO} ≥ 15%, acute exacerbation or death) up to end of study, change in FVC at 4 months
Chien, 2014[51]	USA multi-national	69 (ARTEMIS[52])	24	66.2 (7)	75	69.8 (12.1)	42.1 (11.1)	LOXL2	Overall mortality, lung function decline at 24 months (FVC≥10% with DL_{CO} ≥ 5%, or DL_{CO} ≥ 15% with FVC ≥ 5%), disease progression (mortality, hospitalisation or lung function decline)
	USA multi-national	104 (GAP[53])		66.7 (8.9)	70	66.1 (17.7)	47.8 (18)		
Collard, 2010[54]	South Korea single centre	47 (AE-IPF)	NR	66 (8)	77	75 (18)	64 (20)	KL-6, SP-D	Overall mortality, acute exacerbation
		20 (without AE-IPF)		63 (7	80	84 (19)	74 (22)		
Doubkova, 2016[55]	Czech Republic single centre	18	NR	68.5 (49-79) [a]	56	68 (median)	52 (median)	SP-A, SP-D	Overall mortality, change in FVC
Gui, 2020[56]	China single centre	126	60	NR	75.4	70.1 (17)	50.5 (12.6)	KL-6, CXCL13	Overall mortality, change in FVC over 12 months
Hamai, 2016[39]	Japan single centre	65	31 (26.6-35.4) [b]	69.3 (8.6)	77	75.6 (21.9)	47.1 (15.8)	SP-A, SP-D, CCL-18, KL-6	5-year mortality
Hoyer, 2020[57]	Denmark multi-centre	184	36	NR	NR	NR	NR	PRO-C3, PRO-C6	Overall mortality, disease progression (FVC decline >10% and/or DL_{CO} decline >15% at any time)
Jiang, 2018[58]	China single centre	20 (85 ILD)	12	53.5 (10.5)	59 *	71.1 (17.7) *	49.4 (24.3) *	KL-6	Disease progression (FVC decline ≥ 10% or DL_{CO} decline ≥ 15%, or death) at 12 months
Jenkins, 2015[31]	UK multi-centre	55 (Discovery)	26 (1.6-35.2) [a]	68.5 (9.5)	78	75.9 (23.5)	44.4 (18.3)	ECM-neoepitopes	Overall mortality, disease progression at 12 months (all-cause mortality or >10% FVC decline)
		134 (Validation)	21.2 (0.8-36.2) [a]	70.7 (7.7)	79	78.1 (17.2)	42.1 (13.5)		
Kennedy, 2015[59]	Ireland single centre	13	6	72.6 (10.7)	77	83.3 (26.9)	39.1 (16.1)	SP-D	Change in FVC at 6 months
Kinder, 2009 [60]	USA single centre	82	36 (16-72) [b]	62 (10)	62	64 (18)	54 (16)	SP-A, SP-D	Death or transplantation at 1 year
Maher, 2017[30]	UK multi-centre	106 (Discovery)	36	70.8 (8.3)	78	79 (18.9)	43.3 (14.8)	SP-D, CA125, CA19-9, IGFBP-2, IL-8, ICAM-1	Overall mortality, disease progression at 12 months (all-cause mortality or FVC decline ≥ 10%)
		206 (Validation		72.5 (7.7)	76	81.4 (19.2)	49 (16.9)	SP-D, CA125, CA19-9	
Naik, 2012[61]	USA multi-centre	54 (COMET[62])	18.5	64.3 (8.2)	72	68.5 (15.8)	40. 8 (14.3)	Periostin	Disease progression at 48 weeks (death, acute exacerbation, transplantation, relative FVC decline ≥ 10% or DL_{CO} > 15%)

Neighbors, 2018[29]	multi-national	221 CAPACITY [42]	12	66.9 (7.4)	72	73.4 (13.4)	46.5 (9.4)	CCL-18, CXCL13, YKL-40, Periostin	At 12 months: Disease progression (FVC ≥10% absolute decline or death), change in FVC, death
		244 ASCEND [43]		67.7 (7.2)	77	68.3 (10.9)	43.9 (11.9)		
Ohshimo, 2014[63]	Germany single centre	64 (without AE-IPF)	36 (25.2)	70 (8)	73	68 (15)	44 (14)	KL-6, CCL-18	Acute exacerbation
		13 (with AE-IPF)		67 (5)	85	54 (17)	43 (10)		
Ohta, 2017[64]	Japan multi-centre	60	6.2 (5.8-8.5) [a]	69.2 (8.1)	92	85.8 (20.1)	59.7 (21.8)	Monomeric Periostin, Periostin, KL-6, SP-D	Change in FVC at 6-12 months
Okamoto, 2011[65]	Japan multi-centre	37	NR	66.3 (8.6)	84	80.2 (20)	NR	Periostin	Overall months
Organ, 2019[32]	UK multi-centre	145	34.5 (median)	71.7 (7.7)	81	79.8 (20.4)	48.2 (17.9)	ECM-neoepitopes, collagen synthesis peptides	Overall mortality, disease progression at 12 months (all-cause mortality or >10% FVC decline)
Papiris, 2018[66]	Greece single centre	23 (stable)	12	71 (69-74) [b]	82	72 (60-93) [b]	56 (38-65) [b]	IL-8	Overall mortality at 12 months
		18 (exacerbated)		68.5 (67-78) [b]	61	60 (44-64) [b]	35 (30-36) [b]		
Prasse, 2009[67]	Germany and Italy	72	24	67.2 (8.6)	NR	NR	NR	CCL-18	Overall mortality, change in FVC at 6 months, disease progression at 24 months (>10% FVC decline or death)
Raghu, 2018[46]	multi-national	154	12	67.9 (8.4)	64	71.5 (19.6)	40.9 (15.9)	SP-A, SP-D, CCL-18, KL-6, ICAM-1, Periostin, YKL-40	Disease progression at 52 weeks (FVC decrease ≥10% predicted or DL_{CO} decrease > 15% or lung transplantation or death)
Richards, 2012[47]	USA single centre	140 (Derivation)	22 (19)	67.2 (8.3)	72	62 (19.6)	44.8 (17.1)	IL-8, ICAM-1	Overall mortality, disease progression (FVC relative decline ≥ 10% within any 1 year of follow up)
		101 (Validation	17 (16)	68 (8.7)	66	60.8 (17)	45.4 (19)		
Vuga, 2014[68]	USA single centre	95	> 24	69 (9.7)	74	66 (19.5)	50 (19.5)	CXCL13	Overall mortality

Supplementary Table 1 – Methodological characteristics of all included non-MMP7 studies with baseline participant characteristics and outcome data. Age, baseline FVC and baseline DL_{CO} reported as mean (standard deviation) unless otherwise stated.
DL_{CO}, gas transfer for carbon monoxide; FVC, forced vital capacity; [a] = median and range; [b] = median and IQR
* = reported for all ILD

Study	Study participation	Study attrition	Prognostic factor	Outcome	Confounding	Statistical analysis and reporting
IPD studies						
Hamai, 2016	Moderate	Moderate	Low	Low	Low	Low
Maher, 2017	Low	Moderate	Low	Low	Low	Low
Navaratnam, 2014/Clynick, 2020	Low	Moderate	Low	Low	Low	Low
Neighbors, 2018	Low	Low	Low	Low	Low	Low
Oldham, 2019	Low	High	High	Low	High	Moderate
Raghu, 2018	Low	Low	Low	Low	Moderate	Low
Richards, 2012	Low	Low	Low	Low	Moderate	Low
Rosas, 2018	Low	Low	Low	Low	High	Moderate
Tzouvelekis, 2017	Low	Low	Low	Low	Low	Low
Non-IPD studies						
Bauer, 2017	Low	Low	Moderate	Low	High	Low
Chien, 2014	Low	Low	Low	Low	Moderate	Low
Collard, 2010	Low	Low	Low	Low	High	Low
Doubkova, 2016	Moderate	High	High	High	High	High
Gui, 2020	Low	Low	Low	Moderate	High	Low
Hoyer, 2020	High	High	High	Low	High	High
Jiang, 2018	Low	Low	Low	Low	High	Low
Jenkins, 2015	Low	Moderate	Low	Low	Low	Low
Kennedy, 2015	Moderate	Low	Low	Low	High	Moderate
Kinder, 2009	Low	Low	Low	Low	Low	Low
Naik, 2012	Low	Low	Low	Low	Low	Low
Ohshimo, 2014	Low	Low	Low	Low	Low	Low
Ohta, 2017	Low	High	Low	Low	High	Low
Okamoto, 2011	Low	High	Low	Low	Low	Moderate
Organ, 2019	Low	Moderate	Low	Low	Low	Low
Papiris, 2018	Low	Low	Low	Low	High	Moderate
Peljto, 2013	Low	Low	Moderate	Low	Low	Low
Prasse, 2009	Moderate	Low	Low	Low	Low	Low
Sokai, 2015	Low	Low	Low	Low	High	Low
Vuga, 2014	Moderate	High	Low	High	Low	Low

Supplementary Table 2 – Risk of bias assessment for included studies. The risk of bias across studies was rated as low, moderate or high risk in six categories using the QUIPs tool.

Baseline MMP-7								
Variables	Overall mortality (n=1492)		12-month mortality (n= 1492)		Disease progression (n= 1383)		Change in FVC percent predicted over 12 months (n=891)	
	R^2 (%)	P value	R^2 (%)	P value	R^2 (%)	P value	R^2 (%)	P value
Design (cohort vs. RCT)	0.00	0.747	0.00	0.388	0.00	0.159	0.00	0.988
Assay (ELISA vs. other)	18.45	0.088	25.4	0.075	100	0.013	0.00	0.235
Sample (Serum vs. plasma)	0.00	0.98	0.00	0.483	71.35	0.1875	0.00	0.502
IPF consensus (2011 vs. other)	0.00	0.983	0.00	0.87	100	0.05	N/A	N/A
Centre (single vs. multi)	9.05	0.1995	0.00	0.293	6.23	0.418	91.14	0.195
Publication type (peer reviewed)	0.00	0.922	0.00	0.893	47.51	0.212	0.00	0.659
Change in MMP-7 over 3 months								
Variables	Overall mortality (n=498)		12-month mortality (n=498)		Disease progression (n= 481)		Change in FVC percent predicted over 12 months (n= 481)	
	R^2 (%)	P value	R^2 (%)	P value	R^2 (%)	P value	R^2 (%)	P value
Design (cohort vs. RCT)	0.00	0.916	0.00	0.78	82.84	0.62	0.00	0.716
Assay (ELISA vs. other)	0.00	0.753	84.97	0.07	0.00	0.05	0.00	0.435
Sample (Serum vs. plasma)	0.00	0.56	0.00	0.557	19.2	0.662	0.00	0.716
IPF consensus (2011 vs. other)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Centre (single vs. multi)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Publication type (peer reviewed)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Supplementary Table 3 - Results of meta-regression for variables assessed separated by study outcomes. Sample sizes for each outcome shown (n). R^2 and p values from meta-regression shown where applicable.
N/A, not applicable.

Outcome	The GRADE domains	Ratings for quality of evidence
Baseline MMP-7		
Overall mortality (10 studies; 1492 participants)	Risk of bias	All studies included well-defined participants diagnosed according to international consensus guidelines. Exposure and outcomes were measured objectively and consistently for all participants. Covariates were adjusted for using IPD. Follow up was sufficiently long to enable outcomes to occur.
	Imprecision	Effect sizes in most studies favour MMP-7 as a marker of mortality.
	Inconsistency	Substantial heterogeneity not explained by variability in the factors assessed
	Indirectness	No serious indirectness. All patients had IPF according to consensus criteria and were untreated. MMP-7 was measured at baseline in all studies, and overall mortality measured from IPD.
	Publication bias	No publication bias as indicated by funnel plots and Egger's tests
	Certainty of evidence	Moderate certainty of evidence
12-month mortality (10 studies; 1492 participants)	Risk of bias	All studies included well-defined participants diagnosed according to international consensus guidelines. Exposure and outcomes were measured objectively and consistently for all participants. Covariates were adjusted for using IPD. Follow up was sufficiently long to enable outcomes to occur.
	Imprecision	Imprecision present with wide confidence interval of 0.99-1.78.
	Inconsistency	Substantial heterogeneity not explained by variability in the factors assessed
	Indirectness	No serious indirectness. All patients had IPF according to consensus criteria and were untreated. MMP-7 was measured at baseline in all studies, and 12-month mortality measured from IPD.
	Publication bias	No publication bias as indicated by funnel plots and Egger's tests

	Certainty of evidence	Moderate certainty of evidence
Disease progression (10 studies; 1383 participants)	Risk of bias	All studies included well-defined participants diagnosed according to international consensus guidelines. Exposure was measured objectively and consistently for all participants. Disease progression definition was standardised. Covariates were adjusted for using IPD. Follow up was sufficiently long to enable outcomes to occur.
	Imprecision	Effect sizes consistently favour MMP-7 as a prognostic marker, although confidence intervals commonly cross 1. Overall estimate has appropriately narrow confidence interval supporting MMP-7 as a biomarker of disease progression.
	Inconsistency	No heterogeneity demonstrated.
	Indirectness	No serious indirectness. All patients had IPF according to consensus criteria and were untreated. MMP-7 was measured at baseline in all studies, and disease progression standardised using IPD.
	Publication bias	No publication bias as indicated by funnel plots and Egger's tests
	Certainty of evidence	High certainty of evidence.
Change in FVC at 12 months (8 studies; 891 participants)	Risk of bias	All studies included well-defined participants diagnosed according to international consensus guidelines. Exposure was measured objectively and consistently for all participants. Change in FVC was measured objectively and consistently for all participants. Covariates were adjusted for using IPD. Follow up was sufficiently long to enable outcomes to occur.
	Imprecision	The majority of the studies show MMP-7 to result in a negative change in FVC at 12 months, although confidence intervals cross 0 in all individual studies. Overall confidence interval does not cross 0.
	Inconsistency	No evidence of heterogeneity
	Indirectness	No serious indirectness. All patients had IPF according to consensus criteria and were untreated. MMP-7 was measured at baseline in all studies and change in FVC standardised using IPD.
	Publication bias	No obvious funnel plot asymmetry, although unable to assess statistically due to small number of studies
	Certainty of evidence	High certainty of evidence.

Three-month MMP-7 change		
Overall mortality (4 studies; 498 participants)	Risk of bias	All studies included well-defined participants diagnosed according to international consensus guidelines. Exposure and outcomes were measured objectively and consistently for all participants. Covariates were adjusted for using IPD. Follow up was sufficiently long to enable outcomes to occur.
	Imprecision	Wide confidence intervals in individual studies but narrow confidence interval for overall effect size (no effect)
	Inconsistency	Substantial heterogeneity not explained by variability in the factors assessed
	Indirectness	No serious indirectness. All patients had IPF according to consensus criteria and were untreated. MMP-7 was measured at baseline in all studies, and overall mortality measured from IPD.
	Publication bias	No obvious funnel plot asymmetry, although unable to assess statistically due to small number of studies
	Certainty of evidence	Moderate certainty of evidence
12-month mortality (4 studies; 498 participants)	Risk of bias	All studies included well-defined participants diagnosed according to international consensus guidelines. Exposure and outcomes were measured objectively and consistently for all participants. Covariates were adjusted for using IPD. Follow up was sufficiently long to enable outcomes to occur.
	Imprecision	Wide confidence interval in individual studies but narrow confidence interval for overall effect size (no effect)
	Inconsistency	Heterogeneity not explained by variability in the factors assessed
	Indirectness	No serious indirectness. All patients had IPF according to consensus criteria and were untreated. MMP-7 was measured at baseline in all studies, and 12-month mortality measured from IPD.
	Publication bias	No obvious funnel plot asymmetry, although unable to assess statistically due to small number of studies
	Certainty of evidence	Moderate certainty of evidence

Disease progression (4 studies; 481 participants)	Risk of bias	All studies included well-defined participants diagnosed according to international consensus guidelines. Exposure and outcomes were measured objectively and consistently for all participants. Covariates were adjusted for using IPD. Follow up was sufficiently long to enable outcomes to occur.
	Imprecision	Wide confidence interval in individual studies but narrow confidence interval for overall effect size (no effect)
	Inconsistency	No significant heterogeneity
	Indirectness	No serious indirectness. All patients had IPF according to consensus criteria and were untreated. MMP-7 was measured at baseline in all studies, and overall mortality measured from IPD.
	Publication bias	No obvious funnel plot asymmetry, although unable to assess statistically due to small number of studies
	Certainty of evidence	High certainty of evidence
Change in FVC at 12 months (4 studies; 481 participants)	Risk of bias	All studies included well-defined participants diagnosed according to international consensus guidelines. Exposure was measured objectively and consistently for all participants. Change in FVC was measured objectively and consistently for all participants. Covariates were adjusted for using IPD. Follow up was sufficiently long to enable outcomes to occur.
	Imprecision	Wide confidence interval in individual studies but narrow confidence interval for overall effect size (no effect)
	Inconsistency	Inconsistency present across results from studies
	Indirectness	No serious indirectness. All patients had IPF according to consensus criteria and were untreated. MMP-7 was measured at baseline in all studies and change in FVC standardised using IPD.
	Publication bias	No obvious funnel plot asymmetry, although unable to assess statistically due to small number of studies
	Certainty of evidence	Moderate certainty of evidence.

Supplementary Table 4 – GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach to rate the quality of evidence for the prognostic factor MMP-7

Author (year)	Sample size	Follow up (months)	Effect size (Variance)	Level of adjustment	Effect size reported for
MMP-7 (IPD unavailable)					
Sokai (2015)	57	15	Not significant (NR)	NR	NR
Peljto (2013)	438	19	2.18 (95% CI 1.1-4.32)	b,d,e,h	bio > or < 5.7ng/mL
SP-A					
Kinder (2009)	82	36	HR 3.27 (95% CI 1.49-7.17)	a,b,c,d,e,g	per bio SD
Doubkova (2016)	18	NR	Not significant (NR)	x	bio > or < median (98.1ng/mL)
Hamai (2016)	65	31	HR 1.01 (95% CI 0.99-1.02)	x	continuous
SP-D					
Kinder (2009)	82	36	HR 2.04 (95% CI 0.99-4.22)	a,b,c,d,e,g	per bio SD
Collard (2010)	67	NR	OR 1.23 (95% CI 0.36-4.21)	"Bivariate" - NR	log change in bio
Doubkova (2016)	18	NR	Not significant (NR)	x	bio > or < median (623.1ng/mL)
Hamai (2016)	65	31	HR 1.00 (95% CI 0.99-1.002)	x	continuous
Maher (2017) - *Validation*	206	36	HR 2.72 (95% CI 1.65-4.48)	x	bio > or < 38.7ng/mL
CCL-18					
Prasse (2009)	72	24	HR 7.98 (95% CI 2.49-25.51)	a,b,c,d,e	bio > or < 150ng/mL
Hamai (2016)	65	31	HR 1.007 (95% CI 0.99-1.01)	X	continuous
Neighbors (2018) – *Test*	123	12	OR 4.4 (95% CI 1.13-17.15)	x	bio ≥ or < median
Neighbors (2018) – *Replication*	237	12	OR 3.37 (95% CI 1.17-9.67)	x	bio ≥ or < median
CXCL-13					
Guo (2020)	126	60	HR 1.03 (95% CI 1.02-1.06)	a	bio > or < 62pg/mL

Vuga (2014)	95	>24	HR 14.9 (95% CI 1.1-197.2)	a,b,d,e	bio > or < highest quartile
Neighbors (2018) – *Test*	123	12	OR 2.95 (95% CI 0.76-11.46)	x	bio ≥ or < median
Neighbors (2018) – *Replication*	237	12	OR 6.17 (95% CI 1.75-21.8)	x	bio ≥ or < median
KL-6					
Collard (2010)	67	NR	OR 0.41 (95% CI 0.06-2.93)	"Bivariate" - NR	bio log change
Hamai (2016)	65	31	HR 1.001 (95% CI 1.00-1.002)	a,b,c	continuous
Guo (2020)	126	60	HR 1.83 (95% CI 1.01-3.69)	a	bio > or < 800U/mL
IL-8					
Richards (2012) – *Derivation*	140	22	HR 2.4 (95% CI 1.2-4.79)	a,b,d	bio > or < 0.0029
Richards (2012) – *Validation*	101	17	HR 2.3 (95% CI 0.94-5.64)	a,b,d	bio > or < 0.0097
Papiris (2018)	41	12	OR 1.067 (95% CI 1.01-1.12)	x	per increase of 1pg/mL
CA19-9					
Maher (2017) – *Validation*	206	36	HR 2.95 (95% CI 1.82-4.78)	x	bio > or < 22 U/mL
CA-125					
Maher (2017) – *Validation*	206	36	HR 3.01 (95% CI 1.64-5.54)	x	bio > or < 12 U/mL
LOXL2					
Chien (2014) – *ARTEMIS*	69	24	HR 1.87 (95% CI 0.28-12.45)	d,e,f,h	bio > or ≤ 800pg/mL
Chien (2014) – *GAP*	104	24	HR 2.28 (95% CI 1.18-4.38)	b	bio > or ≤ 700pg/mL
Periostin					
Okamoto (2011)	77	36	Not significant (NR)	x	NR
Neighbors (2018) - *Test*	123	12	OR 3.05 (95% CI 0.79-11.88)	x	bio ≥ or < median
Neighbors (2018) – *Replication*	237	12	OR 1.91 (95% CI 0.72-5.05)	x	bio ≥ or < median
YKL-40					

Neighbors (2018) – *Test*	123	12	OR 1.77 (95% CI 0.53-5.92)	x	bio ≥ or < median
Neighbors (2018) – *Replication*	237	12	OR 2.7 (95% CI 0.94-7.75)	x	bio ≥ or < median
ICAM-1					
Richards (2012) - *Derivation*	140	22	HR 2.6 (95% CI 1.43-4.73)	a,b,d	bio > or < 202.5ng/mL
Richards (2012) – *Validation*	101	17	HR 2.8 (95% CI 1.36-5.76)	a,b,d	bio > or < 300ng/mL
ECM neoepitopes					
Jenkins (2015) –*Discovery* ***BGM***	55	26	HR 1.17 (95% CI 0.53-2.58)	x	two-fold increase in bio value
Jenkins (2015) –*Validation* ***BGM***	134	21	HR 1.34 (95% CI 0.92-1.97)	x	two-fold increase in bio value
Jenkins (2015) –*Discovery* ***C1M***	55	26	HR 1.21 (95% CI 0.66-2.22)	x	two-fold increase in bio value
Jenkins (2015) –*Validation* ***C1M***	134	21	HR 1.62 (95% CI 1.14-2.31)	x	two-fold increase in bio value
Jenkins (2015) –*Discovery* ***C3A***	55	26	HR 1.34 (95% CI 0.95-1.88)	x	two-fold increase in bio value
Jenkins (2015) –*Validation* ***C3A***	134	21	HR 1.91 (95% CI 1.06-3.46)	x	two-fold increase in bio value
Jenkins (2015) –*Discovery* ***C3M***	55	26	HR 2.18 (95% CI 0.95-5.00)	x	two-fold increase in bio value
Jenkins (2015) –*Validation* ***C3M***	134	21	HR 1.56 (95% CI 0.94-2.59)	x	two-fold increase in bio value
Jenkins (2015) –*Discovery* ***C5M***	55	26	HR 1.66 (95% CI 0.95-2.91)	x	two-fold increase in bio value
Jenkins (2015) –*Validation* ***C5M***	134	21	HR 1.07 (95% CI 0.66-1.72)	x	two-fold increase in bio value
Jenkins (2015) –*Discovery* ***C6M***	55	26	HR 1.49 (95% CI 0.86-2.56)	x	two-fold increase in bio value
Jenkins (2015) –*Validation* ***C6M***	134	21	HR 1.39 (95% CI 0.93-2.06)	x	two-fold increase in bio value
Jenkins (2015) –*Discovery* ***CRPM***	55	26	HR 3.74 (95% CI 1.46-9.58)	x	two-fold increase in bio value
Jenkins (2015) –*Validation* ***CRPM***	134	21	HR 1.87 (95% CI 0.98-3.56)	x	two-fold increase in bio value
Jenkins (2015) – *Discovery* ***ELM***	55	26	HR 0.96 (95% CI 0.48-1.92)	x	two-fold increase in bio value
Jenkins (2015) – *Discovery* ***ELM2***	55	26	HR 0.96 (95% CI 0.75-1.24)	x	two-fold increase in bio value

Jenkins (2015) – *Discovery **P3NP***	55	26	HR 1.48 (95% CI 0.67-3.27)	x	two-fold increase in bio value
Jenkins (2015) – *Discovery **VICM***	55	26	HR 1.11 (95% CI 0.83-1.49)	x	two-fold increase in bio value
Collagen synthesis peptides					
Organ (2019) **P1NP**	145	34	HR 0.81 (95% CI 0.6-1.11)	d,e	two-fold increase in bio value
Organ (2019) **PRO-C3**	145	34	HR 1.2 (95% CI 0.74-1.93)	d,e	two-fold increase in bio value
Hoyer (2020) **PRO-C3**	184	36	HR 2.32 (95% CI 1.33-4.04)	a	continuous
Organ (2019) **PRO-C6**	145	34	HR 1.11 (95% CI 0.57-2.16)	d,e	two-fold increase in bio value
Hoyer (2020) **PRO-C6**	184	36	HR 2.18 (95% CI 0.74-4.35)	a	continuous
Organ (2019) **P1NP:C1M**	145	34	HR 0.77 (95% CI 0.6-0.99)	d,e	two-fold increase in bio value
Organ (2019) **PRO-C3:C3M**	145	34	HR 1.17 (95% CI 0.77-1.79)	d,e	two-fold increase in bio value
Organ (2019) **PRO-C6:C6M**	145	34	HR 0.86 (95% CI 0.59-1.26)	d,e	two-fold increase in bio value
Hoyer (2020) **PRO-C6**	184	36	HR 1.8 (95% CI 0.74-4.35)	a	continuous

Supplementary Table 5 – Studies reporting mortality outcomes
x=no adjustments, a=age, b=gender, c=smoking, d=FVC e=DLCO, f= 6MWT, g=race, h=medication

bio, biomarker; HR, hazard ratio; IPD, individual participant data; NR, not reported; OR, odds ratio

Author (year)	Sample size	Follow up (months)	Effect size (Variance)	Level of adjustment	Effect size reported for
SP-D					
Maher (2017) - *Discovery*	106	36	HR 1.01 (95% CI 0.97-1.06)	x	rising vs stable bio over 3 months
Maher (2017) – *Validation*	206	36	HR 0.99 (95% CI 0.59-1.67)	a,b,c,d	rising vs stable bio over 3 months
CA19-9					
Maher (2017) - *Discovery*	106	36	HR 1.02 (95% CI 1.00-1.05)	X	rising vs stable bio over 3 months
Maher (2017) – *Validation*	206	36	HR 1.39 (95% CI 0.79-2.46)	a,b,c,d	rising vs stable bio over 3 months
CA-125					
Maher (2017) - *Discovery*	106	36	HR 1.77 (95% CI 1.39-2.26)	x	rising vs stable bio over 3 months
Maher (2017) – *Validation*	206	36	HR 2.39 (95% CI 1.4-4.08)	a,b,c,d	rising vs stable bio over 3 months
ICAM-1					
Maher (2017) - *Discovery*	106	36	HR 1.002 (95% CI 0.99-1.01)	x	rising vs stable bio over 3 months
IGFBP-2					
Maher (2017) - *Discovery*	106	36	HR 1.02 (95% CI 1.002-1.03)	x	rising vs stable bio over 3 months
IL-8					
Maher (2017) - *Discovery*	106	36	HR 1.02 (95% CI 0.98-1.07)	x	rising vs stable bio over 3 months
ECM neoepitopes					
Jenkins (2015) –*Validation* ***BGM***	134	21	HR 1.07 (95% CI 1.00-1.15)	a,c,d,e	rising vs stable bio over 3 months
Organ (2019) **BGM**	145	34	HR 1.41 (95% CI 0.8-2.47)	a,b,c	rising vs stable bio over 3 months
Jenkins (2015) –*Validation* ***C1M***	134	21	HR 1.01 (95% CI 1.00-1.02)	a,c,d,e	rising vs stable bio over 3 months
Organ (2019) **C1M**	145	34	HR 1.84 (95% CI 1.03-3.27)	a,b,c	rising vs stable bio over 3 months

Jenkins (2015) –*Validation* ***C3A***	134	21	HR 1.05 (95% CI 1.01-1.1)	a,c,d,e	rising vs stable bio over 3 months
Jenkins (2015) –*Validation* ***C3M***	134	21	HR 1.1 (95% CI 1.04-1.17)	a,c,d,e	rising vs stable bio over 3 months
Organ (2019) **C3M**	145	34	HR 2.44 (95% CI 1.39-4.31)	a,b,c	rising vs stable bio over 3 months
Jenkins (2015) –*Validation* ***C5M***	134	21	HR 1.00 (95% CI 1.00-1.00)	a,c,d,e	rising vs stable bio over 3 months
Jenkins (2015) –*Validation* ***C6M***	134	21	HR 1.04 (95% CI 1.01-1.08)	a,c,d,e	rising vs stable bio over 3 months
Organ (2019) **C6M**	145	34	HR 2.19 (95% CI 1.25-3.82)	a,b,c	rising vs stable bio over 3 months
Jenkins (2015) –*Validation* ***CRPM***	134	21	HR 1.33 (95% CI 1.1-1.6)	a,c,d,e	rising vs stable bio over 3 months
Organ (2019) **CRPM**	145	34	HR 2.13 (95% CI 1.21-3.75)	a,b,c	rising vs stable bio over 3 months
Jenkins 2015) – *Validation* ***VICM***	55	26	HR 1.01 (95% CI 0.99-1.03)	a,c,d,e	rising vs stable bio over 3 months
Collagen synthesis peptides					
Organ (2019) **P1NP**	145	34	HR 0.76 (95% CI 0.44-1.3)	a,b,c	rising vs stable bio over 3 months
Organ (2019) **PRO-C3**	145	34	HR 1.62 (95% CI 0.95-2.79)	a,b,c	rising vs stable bio over 3 months
Organ (2019) **PRO-C6**	145	34	HR 1.14 (95% CI 0.67-1.93)	a,b,c	rising vs stable bio over 3 months
Organ (2019) **P1NP:C1M**	145	34	HR 0.73 (95% CI 0.41-1.29)	a,b,c	rising ratio levels
Organ (2019) **PRO-C3:C3M**	145	34	HR 0.83 (95% CI 0.49-1.43)	a,b,c	rising ratio levels
Organ (2019) **PRO-C6:C6M**	145	34	HR 0.55 (95% CI 0.32-0.95)	a,b,c	rising ratio levels

Supplementary Table 6 – Studies reporting short term biomarkers change and their association with mortality

x=no adjustments, a=age, b=gender, c=smoking, d=FVC e=DLCO, f= 6MWT, g=race, h=medication
bio, biomarker; HR, hazard ratio.

Author (year)	Sample size	Timepoint of outcome (months)	Disease progression definition	Effect size (Variance)	Level of adjustment	Effect size reported for
MMP-7 (IPD unavailable)						
Sokai (2015)	57	6	FVC decline ≥10% or DL_{CO} ≥ 15% decline or respiratory failure or death	Not significant (NR)	NR	NR
Bauer (2017)	211	19	FVC decline ≥ 10% or DL_{CO} ≥ 15% decline or respiratory failure or death	HR 2.2 (95% CI 1.4-3.7)	NR	bio < or ≥ 3.8ng/mL
SP-A						
Raghu (2018)	130	12	FVC decrease ≥10% predicted or DL_{CO} decrease > 15% or lung transplantation or death	AUROC 0.61 (90% CI 0.52-0.7)	NR	NR
SP-D						
Collard (2010)	67	NR	Acute exacerbation	361ng/mL vs 294ng/mL (p=0.01)	x	median bio in event and non-event group
Maher (2017) *Discovery*	104	12	All-cause mortality or FVC decline ≥ 10%	GR 1.35 (95% CI 1.1-1.649)	x	bio level in progressive vs. stable group
Maher (2017) *Validation*	204	12	All-cause mortality or FVC decline ≥ 10%	GR 1.35 (95% CI 1.12-1.62)	x	bio level in progressive vs. stable group
Raghu (2018)	130	12	FVC decrease ≥10% predicted or DL_{CO} decrease > 15% or lung transplantation or death	AUROC 0.62 (90% CI 0.53-0.7)	NR	NR
CCL-18						
Prasse (2009)	67	24	FVC decline ≥ 10% prediced or death	OR 6.75 (95% CI 2.52-18.1)	x	bio < or > 150ng/mL
Ohshimo (2014)	77	36	Acute exacerbation	HR 2.92 (95% CI 0.76-11.4)	x	bio > or < 212ng/mL
Neighbors (2018) *Test*	123	12	FVC ≥10% absolute decline, 50m decline in 6MWT or death	HR 1.64 (95% CI 1.04-2.83)	x	'high' vs 'low' bio
Neighbors (2018) *Replication*	237	12	FVC ≥10% absolute decline, 50m decline in 6MWT or death	HR 1.32 (95% CI 0.76-2.13)	x	'high' vs 'low' bio
Raghu (2018)	130	12	FVC decrease ≥10% predicted or DL_{CO} decrease > 15% or lung transplantation or death	AUROC 0.62 (90% CI 0.54-0.71)	NR	bio > or < 150ng/mL

CXCL-13						
Neighbors (2018) *Test*	123	12	FVC ≥10% absolute decline, 50m decline in 6MWT or death	HR 1.23 (95% CI 0.89-1.69)	x	'high' vs 'low' bio
Neighbors (2018) *Replication*	237	12	FVC ≥10% absolute decline, 50m decline in 6MWT or death	Not significant (NR)	x	'high' vs 'low' bio
KL-6						
Collard (2010)	67	NR	Acute exacerbation	1791 U/mL vs 895 U/mL (p=0.003)	x	median bio in event and non-event group
Ohshimo (2014)	77	36	Acute exacerbation	HR 11.8 (95% CI 1.43-97.8)	a,b,c,h	bio > or < 1300U/mL
Jiang (2018)	20	12	FVC decline ≥ 10% or DL_{CO} decline ≥ 15%, or death	OR 1.00 (95% CI 1.00-1.00)	x	continuous bio
Raghu (2018)	130	12	FVC decrease ≥10% predicted or DL_{CO} decrease > 15% or lung transplantation or death	AUROC 0.6 (90% CI 0.51-0.68)	NR	NR
IL-8						
Richards (2012) *Derivation*	140	12	FVC relative decline ≥ 10%	HR 2.00 (95% CI 1.22-3.28)	a,b,d	bio > or < 0.0092ng/mL
Richards (2012) *Validation*	101	12	FVC relative decline ≥ 10%	HR 1.2 (95% CI 0.5-2.85)	a,b,d	bio > or < 0.0092ng/mL
Maher (2017) *Discovery*	104	12	All-cause mortality or FVC decline ≥ 10%	GR 1.51 (95% CI 1.12-2.023)	x	bio level in progressive vs. stable group
CA19-9						
Maher (2017) *Discovery*	104	12	All-cause mortality or FVC decline ≥ 10%	GR 3.12 (95% CI 1.7-5.7)	x	bio level in progressive vs. stable group
Maher (2017) *Validation*	204	12	All-cause mortality or FVC decline ≥ 10%	GR 2.42 (95% CI 1.6-3.65)	x	bio level in progressive vs. stable group
CA125						
Maher (2017) *Discovery*	104	12	All-cause mortality or FVC decline ≥ 10%	Not significant (NR)	x	bio level in progressive vs. stable group
Maher (2017) *Validation*	204	12	All-cause mortality or FVC decline ≥ 10%	GR 1.26 (95% CI 1.05-1.51)	x	bio level in progressive vs. stable group

LOXL2						
Chien (2014) *ARTEMIS*	69	24	Mortality, hospitalisation or lung function decline (FVC≥10% & DL_{CO}≥5%, or DL_{CO} ≥ 15% and FVC≥5%)	HR 5.41 (95% CI 1.65-17.73)	d,e,f,h	bio > or ≤ 800pg/mL
Chien (2014) *GAP*	70	24	Mortality, hospitalisation or lung function decline (FVC≥10% & DL_{CO}≥5%, or DL_{CO} ≥ 15% and FVC≥5%)	HR 1.78 (95% CI 1.01-3.11)	x	bio > or ≤ 700pg/mL
Periostin						
Naik (2012)	50	11	Death, acute exacerbation, transplantation, relative FVC decline ≥ 10% or DL_{CO} > 15%	HR 1.47 (95% CI 1.03-2.1)	a,b,c,d,e	per bio SD
Neighbors (2018) *Test*	123	12	FVC ≥10% absolute decline, 50m decline in 6MWT or death	HR 2.08 (95% CI 1.24-3.47)	x	'high' vs 'low' bio
Neighbors (2018) *Replication*	237	12	FVC ≥10% absolute decline, 50m decline in 6MWT or death	HR 1.75 (95% CI 0.87-2.84)	x	'high' vs 'low' bio
Raghu (2018)	130	12	FVC decrease ≥10% predicted or DL_{CO} decrease > 15% or lung transplantation or death	AUROC 0.6 (90% CI 0.51-0.69)	NR	NR
YKL-40						
Neighbors (2018) *Test*	123	12	FVC ≥10% absolute decline, 50m decline in 6MWT or death	HR 1.39 (95% CI 0.79-2.41)	x	'high' vs 'low' bio
Neighbors (2018) *Replication*	237	12	FVC ≥10% absolute decline, 50m decline in 6MWT or death	Not significant (NR)	x	'high' vs 'low' bio
Raghu (2018)	130	12	FVC decrease ≥10% predicted or DL_{CO} decrease > 15% or lung transplantation or death	AUROC 0.58 (90% CI 0.49-0.67)	NR	NR
ICAM-1						
Richards (2012) *Derivation*	140	12	FVC relative decline ≥ 10%	HR 1.6 (95% CI 1.00-2.56)	a,b,d	bio > or < 202.5ng/mL
Richards (2012) *Validation*	101	12	FVC relative decline ≥ 10%	HR 2.2 (95% CI 1.21-4.01)	a,b,d	bio > or < 262ng/mL
Maher (2017) *Discovery*	104	12	All-cause mortality or FVC decline ≥ 10%	GR 1.29 (95% CI 1.02-1.65)	x	bio level in progressive vs. stable group
Raghu 2018	130	12	FVC decrease ≥10% predicted or DL_{CO} decrease > 15% or lung transplantation or death	AUROC 0.65 (90% CI 0.56-0.73)	NR	NR
ECM neoepitopes						

Jenkins (2015) *D+V cohort* **BGM**	186	12	All-cause mortality or FVC decline ≥ 10%	Not significant (NR)	x	bio level in progressive vs. stable group
Jenkins (2015) *D+V cohort* **C1M**	186	12	All-cause mortality or FVC decline ≥ 10%	Not significant (NR)	x	bio level in progressive vs. stable group
Jenkins (2015) *D+V cohort* **C3M**	186	12	All-cause mortality or FVC decline ≥ 10%	P=0.011 (NR)	x	bio level in progressive vs. stable group
Jenkins (2015) *D+V cohort* **C5M**	186	12	All-cause mortality or FVC decline ≥ 10%	Not significant (NR)	x	bio level in progressive vs. stable group
Jenkins (2015) *D+V cohort* **C6M**	186	12	All-cause mortality or FVC decline ≥ 10%	P=0.013 (NR	x	bio level in progressive vs. stable group
Jenkins (2015) *D+V cohort* **CRPM**	186	12	All-cause mortality or FVC decline ≥ 10%	P=0.014 (NR)	x	bio level in progressive vs. stable group
Jenkins (2015) *D+V cohort* **VICM**	186	12	All-cause mortality or FVC decline ≥ 10%	P=0.033 (NR)	x	bio level in progressive vs. stable group
Jenkins (2015) *D+V cohort* **C3A**	186	12	All-cause mortality or FVC decline ≥ 10%	P=0.003 (NR)	x	bio level in progressive vs. stable group
Jenkins (2015) *Discovery only* **P3NP**	186	12	All-cause mortality or FVC decline ≥ 10%	P=0.63 (NR)	x	bio level in progressive vs. stable group
Jenkins (2015) *Discovery only* **ELM**	186	12	All-cause mortality or FVC decline ≥ 10%	P=0.55 (NR)	x	bio level in progressive vs. stable group
Jenkins (2015) *Discovery only* **ELM2**	186	12	All-cause mortality or FVC decline ≥ 10%	P=0.42 (NR)	x	bio level in progressive vs. stable group
Hoyer (2020) **PROC3**	184	6	All-cause mortality or FVC decline ≥ 10%	P=0.005 (NR)	NR	NR
Hoyer (2020) **PROC6**	184	6	All-cause mortality or FVC decline ≥ 10%	P=0.031 (NR)	NR	NR

Supplementary Table 7 – Studies reporting disease progression outcomes including definition of disease progression outcome used and effect sizes reported.

x=no adjustments, a=age, b=gender, c=smoking, d=FVC e=DL_{CO}, f= 6MWT, g=race, h=medication, NR=not reported

bio, biomarker; AUROC; area under the receiver operating characteristics; $DL_{CO,}$ gas transfer for carbon monoxide; FVC, forced vital capacity; GR, group ratio; HR, hazard ratio; IPD, individual participant data; NR, not reported; OR, odds ratio; 6MWT, 6-minute walk test;

Author (year)	Sample size	FVC change measured at (months)	Effect size (Variance)	Level of adjustment	Effect size reported for
MMP-7 (IPD unavailable)					
Bauer (2017)	195	4	p=0.004 (NR)	x	baseline bio correlation with %pred FVC change
SP-A					
Doubkova (2016)	18	NR	155.8 ng/mL vs 87.15 ng/mL; p=0.01	x	baseline bio in PFT "improvement" vs "stabilisation"
SP-D					
Doubkova (2016)	18	NR	861.4ng/mL vs. 802.8ng/mL; p=0.76	x	baseline bio in PFT "improvement" vs "stabilisation"
Kennedy (2015)	13	6	r= -0.64 (95% CI -0.89 to -0.08)	x	baseline bio correlation with %pred FVC change
Ohta (2017)	60	6-12	r= 0.09 (p>0.05)	x	baseline bio correlation with %pred FVC change
CCL-18					
Neighbors (2018) – *Test*	123	12	-3.1% (p=0.03)	x	%pred FVC change in baseline bio ≥ or < median (411.5ng/mL)
Neighbors (2018) – *Replication*	237	12	-3.6% (p=0.004)	x	%pred FVC change in baseline bio ≥ or < median (458.6ng/mL)
Prasse (2009)	67	6	r=0.54 (p<0.0001)	x	baseline bio correlation with %pred FVC change
CXCL-13					
Guo (2020)	126	12	r= 0.56 (p<0.001)	x	baseline bio correlation with %pred FVC change
Neighbors (2018) – *Test*	123	12	-3.2% (p=0.06)	x	%pred FVC change in baseline bio ≥ or < median (87.9ng/mL)
Neighbors (2018) – *Replication*	237	12	-3.7% (p=0.05)	x	%pred FVC change in baseline bio ≥ or < median (88.7ng/mL)
KL-6					
Guo (2020)	126	12	r= 0.71 (p<0.001)	x	baseline bio correlation with %pred FVC change
Ohta (2017)	60	6-12	r= 0.09 (p>0.05)	x	baseline bio correlation with %pred FVC change
Okamoto (2011)	26	6	Not significant (NR)	x	baseline bio correlation with %pred FVC change

Periostin					
Neighbors (2018) – *Test*	123	12	-3.6% (p<0.001)	x	%pred FVC change in baseline bio ≥ or < median (67.8ng/mL)
Neighbors (2018) – *Replication*	237	12	-2.5% (p=0.19)	x	%pred FVC change in baseline bio ≥ or < median (65.4ng/mL)
Ohta (2017)	60	6-12	r= -0.43 (p<0.01)	x	baseline bio correlation with %pred FVC change
Okamoto (2011)	26	6	r= -0.50 (p<0.01)	x	baseline bio correlation with %pred FVC change
YKL-40					
Neighbors (2018) – *Test*	123	12	-2.4% (p=0.04)	x	%pred FVC change in baseline bio ≥ or < median (100.3ng/mL)
Neighbors (2018) – *Replication*	237	12	-1.5% (p=0.70)	x	%pred FVC change in baseline bio ≥ or < median (109.5ng/mL)

Supplementary Table 8 – Studies reporting association with baseline biomarkers and change in forced vital capacity (FVC).
bio, biomarker; x = no adjustments

IPD, individual participant data.

Author (year)	Sample size	Timepoint of outcome (months)	Disease progression definition	Effect size (Variance)	Level of adjustment	Effect size reported for
MMP-7 (IPD unavailable)						
Bauer et al (2017)	211	"Study period"	FVC ≥10% decline, DL_{CO} ≥ 15%, acute exacerbation or death	OR 1.9 (95% CI 1.2-3.0)	NR	Two-fold change in bio over 4 months
SP-D						
Maher et al (2017) *Discovery*	106	12	All-cause mortality or FVC decline ≥ 10%	p=0.029	x	rising vs stable bio over 3 months
Maher et al (2017) *Validation*	206	12	All-cause mortality or FVC decline ≥ 10%	Not significant (NR)	x	rising vs stable bio over 3 months
CXCL-13						
Vuga et al (2014)	95	>24	Respiratory failure	HR 7.2 (95% CI 1.3-40.0)	x	bio "increase greatest vs. less increased" (time not specified)
CA19-9						
Maher et al (2017) *Discovery*	106	12	All-cause mortality or FVC decline ≥ 10%	p<0.001	x	rising vs stable bio over 3 months
Maher et al (2017) *Validation*	206	12	All-cause mortality or FVC decline ≥ 10%	Not significant (NR)	x	rising vs stable bio over 3 months
CA125						
Maher et al (2017) *Discovery*	106	12	All-cause mortality or FVC decline ≥ 10%	p=0.041	x	rising vs stable bio over 3 months
Maher et al (2017) *Validation*	206	12	All-cause mortality or FVC decline ≥ 10%	p=0.0028	x	rising vs stable bio over 3 months
KL-6						
Jiang et al (2018)	20	12	FVC decline ≥ 10%, DL_{CO} decline ≥ 15% or death	OR 3.61 (95% CI 1.05-6.22)	a,b,c,d,e	Change in KL-6 (not otherwise specified)

Supplementary Table 9 – Studies reporting short term biomarkers change and their association with disease progression

x=no adjustments, a=age, b=gender, c=smoking, d=FVC e=DL_{CO}, f= 6MWT, g=race, h=medication, NR=not reported
bio, biomarker; $DL_{CO,}$ gas transfer for carbon monoxide; FVC, forced vital capacity; GR, group ratio; HR, hazard ratio; IPD, individual participant data; NR, not reported; OR, odds ratio